EXHIBIT C

VALSARTAN LITIGATION
REPORT OF MICHAEL BOTTORFF, Pharm. D.

This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions I offer in this report is given to a reasonable degree of scientific certainty and is based on the methods and procedures of science, my knowledge of recognized scientific principles and methodology reasonably relied upon by members of my profession, the materials and literature I have reviewed in connection with this litigation, as well as my education, training, knowledge, and experience. Citations to specific reference material are offered in this report, where I believe it necessary to cite a specific source. Otherwise, my opinions are derived from a combination of reference sources, my own experience, and general scientific knowledge. The facts and data set forth herein are the types of facts and data that I and other experts in the fields of pharmacology and pharmacokinetics reasonably rely upon. Each opinion in this report is offered to articulate a sufficiently reliable basis for my opinions concerning this case. This report is not meant to be an exhaustive recitation of all of my opinions in this case as I understand my opinions will be more fully explored at my deposition.[1]

I. CREDENTIALS AND EXPERIENCE

I am currently employed at the College of Pharmacy at Manchester University in Ft. Wayne, Indiana as an adjunct professor, and at the University of Cincinnati in the same faculty position. I have been employed by Manchester University since 2015, and hold the rank of Full Professor. A copy of my current *curriculum vitae* detailing my education, academic and

[1] This report contains my opinions regarding general causation only. This report is not intended to be an exhaustive recitation of all of my opinions in this litigation, and I expressly reserve the right to amend or supplement this report to offer additional opinions, including opinions on liability, specific causation, damages, or other defenses, at the appropriate stage of litigation.

professional experience, editorial services, professional affiliations, and publications, is attached as **Exhibit A**. I received a Bachelor of Science degree with honors in Industrial Management from the Georgia Institute of Technology in 1976. I completed my Doctor of Pharmacy in 1981 at the University of Kentucky. My postdoctoral training (1981-1983) was at the Albert B. Chandler Medical Center at the University of Kentucky in the College of Pharmacy where I was the chief resident.

In my current position, I teach or have taught medical students, pharmacy students and residents pharmacology, including cardiovascular pharmacology. I provide information on how pharmaceutical drugs work in the body and how drugs interact with the body's systems so they may better understand how to select the best drug for a particular patient's needs. Since their introduction into the U.S. market, sartans are drugs that I have taught my medical and pharmacy students and/or residents when discussing the treatment of hypertension and heart failure. “Sartans” are Angiotensin Receptor Blockers (“ARB”), including, for example, valsartan, losartan, and irbesartan (hereafter “sartans”). I also instruct on issues related to pharmacology, metabolism, clinical benefit, toxicities, and drug interactions for a variety of pharmaceutical drugs, including for the sartans described above. I have a 30 year history of rounding on hospital in-patients with cardiologists treating patients receiving drug therapy for hypertension and heart failure, and I have lectured extensively on cardiovascular topics for nearly 40 years.

In addition to my current teaching responsibilities, I continue to author textbooks and journal articles, as well as give presentations on cardiac pharmacotherapy and pharmacologic principles. I have been awarded numerous research grants and have published 36 original research articles in peer-reviewed journals in my field, along with dozens of abstracts related to

cardiovascular pharmacotherapy and pharmacokinetics. Most of these studies have incorporated the use of pharmaceuticals, which has required specific knowledge of the pharmacokinetics and pharmacodynamics of these drugs.

Prior to accepting my position at Manchester University, I was a Professor and Chair of the Department of Pharmacy Practice for 4 years at the South College School of Pharmacy, and held a similar position prior to that at the School of Pharmacy at the University of Charleston in the Department of Pharmacy Practice. I was also Co-Director, PharmUC, a Cardiovascular Risk Reduction Clinic offering anticoagulation, lipid, diabetes, and hypertension ("HTN") management services. My research has focused on cardiac and vascular function, and how cardiovascular drugs affect function. I have lectured nationally and internationally on antihypertensive drugs and drugs for heart failure, including their pharmacokinetic and pharmacodynamic properties. Prior to working at the University of Charleston, I was a professor of Clinical Pharmacy at the College of Pharmacy for 20 years at the University of Cincinnati. Prior, I also served as faculty at the University of Tennessee where I lectured on the practice of Clinical Pharmacy using cardiovascular drugs.

During my career, I have served on advisory boards and national speaker bureaus for several of the pharmaceutical companies that make sartans, including Merck (lostaran), Bristol Meyers-Squibb (irbisartan), and Novartis (valsartan). I have received numerous awards and honors in the field of Clinical Pharmacy, and published original research, review articles and book chapters in peer-reviewed journals and books, much of which involved investigation of drug metabolism and pharmacokinetics. Additional presentations and publications on this subject are reflected on my CV attached here. I have also participated in numerous pre-market

drug studies on the mechanisms of action, absorption and distribution of pharmaceuticals in the body, and evaluation of new drugs for drug-drug interaction.

II. DISCLOSURES

I have been asked on behalf of Defendants to provide an independent evaluation of the pharmacokinetics of valsartan and N-nitrosodimethylamine ("NDMA") and N-nitrosodiethylamine ("NDEA") in this case. I will offer opinions on the background of NDMA and NDEA and valsartan, as well as general principles of pharmacokinetics, including the related topics of pharmacology, pharmacodynamics, and drug interactions. I will offer opinions on the pharmacokinetics and metabolic fate, including the absorption, metabolism, distribution, and elimination, of valsartan as well as NDMA/NDEA. I will opine on whether the trace amounts of NDMA/NDEA found in valsartan could create an independent or increased risk of the cancers alleged by Plaintiffs. I will also opine on the clinical impact of stopping valsartan.

The materials I have reviewed in connection with this matter are listed on **Exhibit B** attached here. I reserve the right to supplement this list, as well as to amend and supplement the opinions expressed in this report. I reserve the right to modify this report and my opinions as additional information is provided, including but not limited to additional discovery, records, expert reports, and the depositions of fact and expert witnesses. I also reserve the right to testify within my area of expertise in response to testimony from any of the plaintiffs' experts, whom I understand have not yet been deposed, or in later phases of the case involving liability, specific causation, damages or otherwise.

In addition to documents identified in **Exhibit B**, my opinions are based on my knowledge, research and experience with the pharmacology and pharmacokinetics of drugs.

My customary fee for professional services, including my review and testimony in this matter, is $500 per hour. In the last four years, I have testified in Polt et al. v. Sandoz Inc., No. 2:16-cv-02362-ER, U.S. District Court for the Eastern District of Pennsylvania.

III. METHODOLOGY FOR REPORT

In order to conduct research, write published manuscripts, give national/international presentations and teach to pharmacy, medicine and nursing students, I rely on the retrieval, analysis and synthesis of the medical and scientific literature. I used this same process to review the medical and scientific literature on the relevant issues in this litigation—and 40 years' experience conducting such processes—to derive my opinions.

I have independently conducted a literature review and research on the relevant issues in this litigation, including the metabolic fate, metabolism, and distribution of NDMA/NDEA and valsartan.

IV. BACKGROUND AND OPINIONS

1. Background on NDMA/NDEA Found in Valsartan

Valsartan, along with losartan and irbesartan, are FDA-approved prescription drug products that fall within the angiotensin receptor blockers (ARBs) drug class, used for the treatment of hypertension, or high blood pressure, and heart failure. Valsartan has been used for many years to safely and effectively treat hypertension and heart failure. Valsartan is available in tablet and liquid forms and is ingested orally. It is commonly prescribed in dosage strengths of 40 mg, 80 mg, 160 mg, or 320 mg.

This litigation arises from a situation in which the unexpected impurities NDMA and later NDEA were found in certain lots of valsartan made by various manufacturers leading to recalls beginning in or around June 2018 and November 2018, respectively.

When Zhejiang Huahai Pharmaceutical Co. Ltd. ("ZHP") became aware of the NDMA impurity, ZHP tested certain of its active pharmaceutical ingredient ("API") batches and determined that the levels of NDMA found ranged from 3.4 ppm to 120 ppm, with an average of 66.5 ppm. The U.S. Food and Drug Administration ("FDA") published NDMA testing results for finished dose products that were manufactured using various manufacturers' APIs. The FDA's publication included several valsartan products containing NDMA, in varying amounts:

Table 1 – FDA's Testing of Valsartan for NDMA[2]

Company	Product (tablets)	Lots Tested	NDMA level micrograms – (mcg)/tablet (midpoint)	NDEA level micrograms – (mcg)/tablet (midpoint)
Aurobindo Pharma Ltd	Amlodipine 10mg/Valsartan 320 mg	VKSA18005-A, VKSA18007-A, VKSA18001-A	Below LOD	0.02-0.09 (0.055)
Aurobindo Pharma Ltd	Valsartan 320mg	VUSD17008-A, VUSD17001-A, VUSD17009-A	Below LOD	0-0.05 (0.025)
Aurobindo Pharma Ltd	Valsartan 320mg/HCT 25mg	HTSB18001-A, HTSB18028-A,	Below LOD	0.02-0.19 (0.105)

[2] *See* FDA, *Laboratory Analysis of Valsartan Products*, FDA.gov, *available at* https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products (last updated May 2, 2019) (midpoint amounts added in parentheticals).

		HTSB18029-A		
Hetero Labs Ltd	Valsartan 320mg	VLS18049, VLS18051, VLS18050	0.33-0.44 (0.385)	Below LOD
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg	3079709, 3077618, 3079708	Below LOD	0.04-0.11 (0.075)
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	2008702	Below LOD	0.05
Mylan Pharmaceutical Inc.	Valsartan 320mg	3080009, 3080010, 3079205	Below LOD	0.07-0.16 (0.115)
Mylan Pharmaceutical Inc.	Valsartan 320mg/HCT 25mg	3084886, 3093804, 3084862	Below LOD	0.20-0.38 (0.29)
Prinston Pharmaceutical	Valsartan 320mg	344B18027, 344B18028, 344B18029	15.18-16.30 (15.74)	Below LOD
Prinston Pharmaceutical	Valsartan 320mg/HCTZ 25mg	611B18025, 611B18026, 611B18027	13.18-20.19 (16.69)	Below LOD
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg	26X053, 26X054, 26X055, 26X051, 26X044, 26X048	Below LOD	0-0.03 (0.015)
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	22X045, 22X046, 22X047, 22X038, 22X041	Below LOD	0-0.03 (0.015)
Teva Pharmaceuticals	Valsartan 320mg	1240425A, 1247282M	7.92-16.55 (12.24)	Below LOD
Teva Pharmaceuticals	Valsartan 320mg/HCTZ 25mg	1217576M, 1217577M, 1217578M	6.94-10.35 (8.65)	0-0.77 (0.385)

Torrent Pharmaceuticals	Amlodipine 10mg/Valsartan 320 mg/HCTZ 25mg	BBX2E001, BBX2E002, BBX2E003	10.24-11.53 (10.89)	Below LOD
Torrent Pharmaceuticals	Valsartan 320mg	BV48D001, BV48D002	0.56-0.62 (0.59)	1.12-1.22 (1.17)
Torrent Pharmaceuticals	Valsartan 160mg	BV47D001	0.45	1.31

For values that report a range for any manufacturer, I have included (in parentheses) the calculated midpoint for that range of values.

2. Principles of Pharmacokinetics

a. What is Pharmacokinetics

Pharmacokinetics is the description of what happens to a drug/chemical as it passes through the human body. The steps involved in this journey through the body are absorption, distribution, metabolism, and elimination, often abbreviated ADME. For the majority of drugs, these processes have been clearly identified and expressed in mathematical terms that describe the rate and extent of each step.[3]

i. *Absorption: the various ways in which xenobiotics enter the body*

Most drugs are introduced into the body by either an oral (by mouth) or injected (intravenously or IV usually). Other drugs may be introduced through inhalation, transdermally, sublingually or rectally. Absorption, metabolism, distribution, and elimination are dependent on the route of administration; thus, I will address absorption with oral and non-oral routes of administration in turn.

[3] Caldwell, *An introduction to drug disposition: the basic principles of drug absorption, distribution, metabolism and excretion* (1995); Bottorff MB et al., *Drug concentration monitoring*, in: Progress in clinical biochemistry and medicine, Springer-Verlag, Heidelberg 1-16 (1988).

Oral Administration:

When administered orally, for the drug to eventually reach the blood stream (the systemic circulation), the drug must first be released from the dosage form (e.g., tablet, capsule) then absorbed across the gastrointestinal tract. Although most drugs are released from their dosage form in the acidic environment of the stomach, the stomach is not the most common area for absorption into the body. The design of the upper small intestine is such that most drugs (and nutrients) are absorbed there. Once absorbed across the small intestine, adjacent blood supply transports the drug into the portal circulation directly into the liver. The liver is a most complex organ providing a number of important physiologic functions that include drug metabolism as a detoxification step. This is a protective system that gives the liver a chance to metabolize/detoxify ingested compounds before releasing the drug and/or its metabolites into the systemic circulation for ultimate elimination. This metabolic step prior to a drug reaching the systemic circulation is termed pre-systemic metabolism or first-pass metabolism. Graphically, for illustration purposes, this process is seen here:

Figure 1.

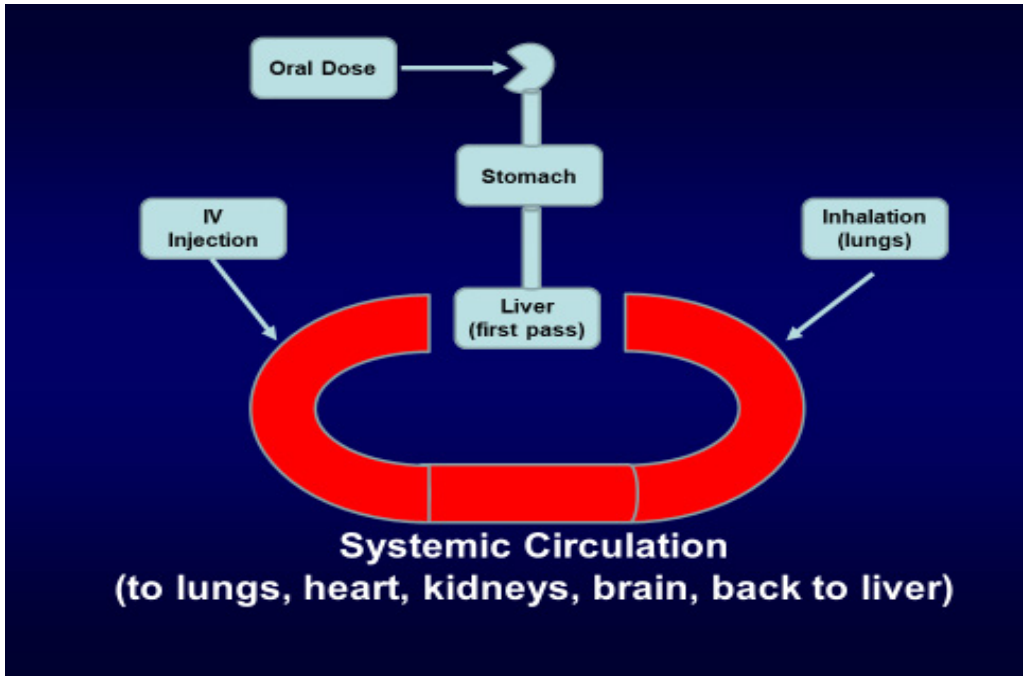
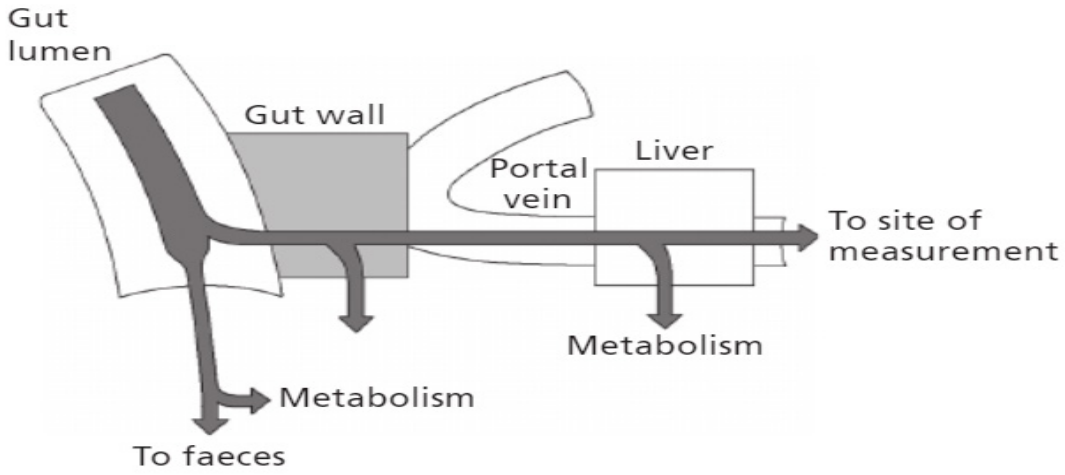


Figure 2.[4]



[4] Thelen K et al., *Cytochrome P450-mediated metabolism in the human gut wall*, J. Pharm. Pharmacol. 61:541-558 (2009).

Non-Oral Administration:

Drugs administered by non-oral routes are often given to "skip" the process of first-pass metabolism. This is particularly important for drugs whose first-pass metabolism is so extensive, that very little orally administered drugs reach the systemic circulation and would have little systemic pharmacologic effect. The non-oral routes of drug administration have in common that they are either injected or rapidly absorbed directly into the systemic circulation without first undergoing any first-pass metabolism. Metabolism then would occur when blood flow takes the drug to an organ with metabolizing activity (e.g., liver, kidney, lung). Thus, only when an oral dose of drug is high enough to overcome metabolic capacity during first-pass metabolism would systemic drug concentrations reach other organs in a fashion similar to giving the drug by a non-oral route.

ii. Metabolism is route-dependent

Oral Administration:

A major function of the liver is to metabolize drugs, which are usually fat soluble, to a metabolite that is more water soluble and more easily eliminated from the body through the kidney. These metabolism steps are divided into two main types, Phase 1 and Phase 2 reactions. Phase 1 metabolic reactions are accomplished by a super family of metabolizing enzymes called the cytochrome P450 system ("CYP").[5] There are over 50 individual CYP enzyme identified in humans. Each individual CYP has a specific role in metabolism of a specific drug, called substrate specificity, so the individual CYPs have a name that identifies its specificity. Examples include CYP3A4, CYP2D6, CYP2E1 and so on. The majority of these CYPs

[5] McDonnell AM, Dang CH, *Basic review of the cytochrome p450 system*, J. Adv. Pract. Oncol. 4(4):263-268 (2013).

are found in the liver, however many of the CYPs are also located in the gut wall where some drug metabolism may occur prior to reaching the liver, depending on the presence or absence of that individual CYP in the gut wall. Thus, one component of first-pass metabolism (see Figure 2) may occur as drugs are absorbed across the gut wall prior to another round of metabolism by the liver. Other sources of CYP are the lungs, kidney, and brain, where local drug metabolism could occur if the parent compound reaches that organ by overloading the capacity of first-pass metabolism.

Phase 2 reactions are termed conjugation reactions in that the parent compound has a chemical structure added to the drug to make it more water soluble for renal elimination. These include glucuronidation, sulfation, acetylation, and others. In many cases, a drug is first metabolized by the CYP system in a Phase 1 reaction then undergoes a second round of Phase 2 metabolism, rendering the drug's metabolites more readily excreted by the kidney.

Non-Oral Administration:

Non-oral routes of drug administration deliver the drug more directly into the systemic circulation (see Figure 1) and bypass first-pass metabolism. For drugs having a high rate of first pass-metabolism, for example, the IV dose may be several fold lower than an oral dose given to provide the same systemic exposure and pharmacologic effect. There are many examples of these type of drugs in the field of cardiology, such as lidocaine, metoprolol, nitroglycerin and diltiazem. For example, an oral dose of metoprolol of 100-200mg produces a similar effect to an IV dose of only 5mg, due to high first-pass metabolism. Thus, when evaluating the relationship between a drug dose and some pharmacologic or toxic response, an IV or inhaled

dose would be expected to reach many different target organs. An oral dose of the same strength may not do so if the dose is below the first-pass metabolic capacity.

iii. Distribution

Oral Administration:

Drug distribution occurs if drug gets by first-pass metabolism and reaches the systemic circulation, where it is transported by the blood stream to various organs and tissues. For a drug with higher affinity for plasma proteins (protein binding), the amount of drug escaping first-pass metabolism would have a more limited tissue distribution as the drug prefers to remain bound to the proteins in the blood stream itself. Either unbound drug, or drugs with little to no protein binding, are then free to interact with the various tissues and organs where the clinical effects are seen. The drug then binds to receptors, enzymes or other target sites that result in the action (beneficial, toxic) of that drug. This is termed the drug's pharmacology or pharmacodynamics, or the effect of the drug on the body. In some cases, the drug metabolites actually have activity at a target site as well.

Non-Oral Administration:

Drug distribution begins immediately with non-oral administration—for example, as soon as an IV dose of a drug is administered or a drug is inhaled—and elimination follows as the drug reaches organs with drug metabolism capacity. The rate of drug elimination (half-life) will then be a reflection of the drug's distribution (volume of distribution) and the sum of the metabolism in all the different tissues and organs (clearance).

iv. Elimination

Oral Administration:

Drugs or their metabolites are usually filtered by the kidney then eliminated from the body in urine. Some drugs may be eliminated in the feces; this could occur for a portion of a drug that is never completely absorbed across the gut wall or for a drug that is incorporated in the liver into the bile and secreted through the bile duct into the gall bladder, which dumps bile into the small intestine.[6] Other less common routes of elimination include in air vapor from the lung or in sweat.

Non-Oral Administration:

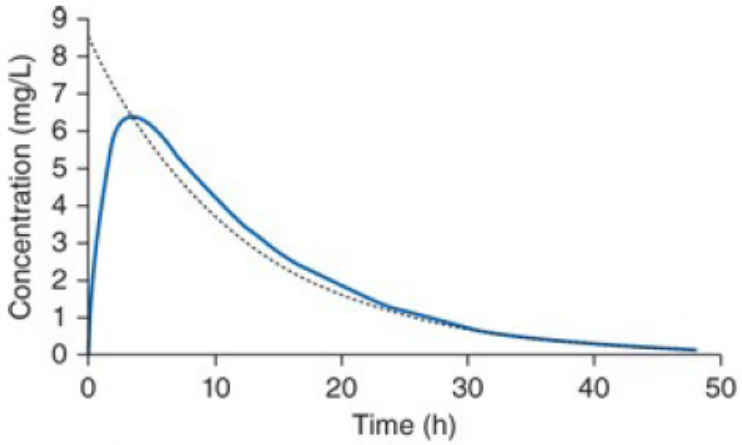
Once drugs administered by non-oral routes reach the blood stream, they are circulated into and then out of target or metabolizing tissues/organs. Depending on the dose and the efficiency of metabolism in each organ, the drug keeps "re-cycling" through repeat rounds of metabolism until the drug is completely eliminated. This is called the terminal elimination phase for a drug, and usually follows first order kinetics in that a constant percentage of drug is removed per time. A terminal half-life can then be calculated as a reflection of this rate of decline.

b. Mathematically Characterizing Pharmacokinetic Processes

Once an oral or injected drug has been administered, blood and/or urine samples can be collected and the serum analyzed for a drug over a specified period of time to numerically characterize the various steps in the ADME process. This produces a concentration versus time plot as in Figure 3 below.

[6] Dobrinska MR, *Enterohepatic circulation of drugs*, J. Clin. Pharmacology 29:577-80 (1989).

Figure 3.[7]



For an orally administered drug, represented by the solid blue line in Figure 3, there will be a rise in serum concentrations reflecting the rate of absorption until the rate of distribution and elimination exceeds the rate of absorption and drug concentrations begin to fall. The highest measured drug concentration is called the peak and the rate of drug decline in the serum can be reflected by something called the half-life—that is, the time it takes for a drug concentration to be cut in half. There are three additional points of interest in Figure 3 above: 1) the dashed line represents an injected dose of a drug (or some other non-oral route), which would have no absorption phase and would also bypass the first-pass metabolism of that drug, making it more readily distributed to tissues outside the liver; 2) the area under the concentration time curve ("AUC") is a reflection of systemic exposure to the drug and related to the overall extent of bioavailability in the case of an orally administered drug (bioavailability would essentially be 100% for a drug administered by the IV route); and 3) an orally administered drug with

[7] Bauer LA, Applied Clinical Pharmacokinetics Ch. I: *Basic Concepts* (3d ed. 2014).

extensive first-pass metabolism would not result in significant extrahepatic distribution, elimination or pharmacologic effect and no or little drug would be measured in the blood after administration.

c. Linear vs. Non-Linear Pharmacokinetics

When doubling the dose of a given drug results in a doubling of the AUC, or systemic exposure, that drug is deemed to exhibit linear pharmacokinetics. Since drug dose and elimination are the primary determinants of the overall AUC, a drug displaying linear pharmacokinetics implies that the metabolic process for that drug has not been exceeded. If, however, the increase in drug dose results in a disproportionately larger increase in AUC, then the metabolic capacity of the drug has been exceeded and a larger than proportional increase in systemic drug exposure will result. This is often seen with drugs having significant first-pass metabolism; once the metabolic capacity of the liver is exceeded by a high enough dose, then a disproportionate rise in serum concentrations and systemic exposure would result. When drugs are given in doses that do not exceed the metabolic capacity, the elimination rate is constant and it takes the same amount of time to eliminate the drug based on its half-life. This is termed first order elimination and 95% of drugs are given in doses that result in a first order pharmacokinetic profile. For example, for a drug with a 6 hour half-life, it would take 6 hours for drug serum concentrations to reduce from 100 nanograms per milliliter to 50 nanograms per milliliter and the same 6 hours to reduce from 10 nanograms per milliliter to 5 nanograms per milliliter.

However, if the elimination system has been saturated with a higher dose, then the dose has exceeded the metabolic capacity for that drug and a maximum amount of drug will be

eliminated in a fixed rate until the concentrations go below the maximum threshold, and first order pharmacokinetics takes over. Thus, doses that produce linear pharmacokinetics are eliminated in a first order fashion, and doses above the metabolic capacity display non-linear elimination and zero order pharmacokinetics.

d. Pharmacokinetic Parameters

As a result of mathematically describing the pharmacokinetics of a drug, there are several calculated parameters unique to an administered drug at a particular dose. The rate of elimination is termed half-life—the time it takes for drug concentrations to fall by 50% during a first order pharmacokinetic process. The peak concentration, Cmax, reflects the highest measured drug concentration after an oral dose and is a reflection of the rate of absorption. The AUC is a measure of the overall systemic exposure to a drug. When observed serum concentrations are compared to the dose given, there is an apparent volume of distribution, Vd, usually expressed in liters, reflecting a hypothetical volume that the drug dose was distributed in. It is a reflection of how much the drug distributes into body. Bioavailability is another term that reflects what percent of an orally administered drug reaches the systemic circulation. Drugs with extensive first-pass metabolism will have a lower bioavailability than drugs that have less extensive first-pass metabolism. Finally, when comparing the bioavailability of one drug to another, as in the case of a generic drug versus the original drug, the term bioequivalence is used to reflect how similar one drug product is compared to another, utilizing the Cmax and AUC as markers of rate and extent of bioavailability.

All of the pharmacokinetic terms may be determined after a single dose or in some cases after multiple doses. When enough multiple doses are administered such that the rate of

drug being given is matched by the rate drug elimination, then the drug is said to be at "steady state," and the rise and fall of drug concentrations with each dose will be the same, dose after dose.

e. Mechanisms of Drug Interactions

Drug-drug interactions can occur when two co-administered compounds interfere with the ADME of one or both of the drugs administered together. Drug concentrations could rise, leading to drug toxicity, or fall, leading to a loss of drug effect. Given that the vast majority of administered drugs are lipid soluble to varying degrees and require the CYP450 system for elimination, competition for a specific CYP enzyme is the most common mechanism of drug interaction.[8] The drug with higher affinity for the specific CYP enzyme will be preferentially metabolized to the detriment of the other drug, increasing its drug levels to potentially dangerous levels. However, for drugs not as dependent on CYP enzymes, or for drugs with different CYP pathways, no significant drug interaction would be expected. Thus, the identification of each compound's specific metabolic fate is important to predicting when two co-administered compounds might interact, or not.

f. Importance of Route of Administration

From the above description of pharmacokinetic processes, it is evident that the ultimate disposition of a compound will depend, to a large extent, on both the dose and the route of administration. This is most important for compounds with a high first-pass extraction, where

[8] Bottorff MB, *Safety considerations of statin therapy*, Cardiology Review 16:5-9 (1999); Worz CR & Bottorff MB, *The role of cytochrome P450-mediated drug-drug interactions in determining safety of statins*, Expert Opin. Pharmacother. 7:1119-27 (2001); Bottorff MB, *Statin safety and drug interactions: clinical implications*, Am. J. Cardiol. 97:27C-31C (2006).

the dose administered orally will determine ultimate drug distribution and metabolism. If the dose is below the capacity of the liver to efficiently extract the drug, then what escapes the liver to the systemic circulation will be metabolites and very little parent compound. Only when the dose exceeds first-pass metabolism capacity, will unchanged drug or compound be systemically available for distribution through the blood stream, leaving the liver and being delivered to other tissues and organs. There are numerous examples of this in the medical literature; lidocaine, an anesthetic and antiarrhythmic drug, can only be administered intravenously for its antiarrhythmic effect because oral use is almost completely cleared by first-pass metabolism. Nitroglycerin, a long-time drug for angina, is most effective given intravenously, sublingually or transdermally, routes of administration that bypass the liver's first-pass metabolism. Only when given in large oral doses can nitroglycerin be an effective antianginal drug by overloading the first-pass metabolism of the compound. Thus, for drugs having a high first-pass metabolism, more widespread drug distribution to organs beyond the liver would be seen with non-oral routes of administration, such as sublingual, intravenous, and inhalation, among others.

3. Pharmacology vs. Pharmacokinetics vs. Pharmacodynamics

As explained above, a basic description of pharmacokinetics is how the body handles an administered compound, resulting in a mathematical characterization of these processes using ADME. Pharmacodynamics is what the drug or compound does to the body. Included in pharmacodynamics is how a particular drug works, through what mechanism(s). That is the drug's pharmacology. For example, is it a blood pressure lowering drug acting on the renin-angiotensin system, or a blood pressure drug blocking the body's beta-receptors?

My 40 year career in clinical pharmacy has incorporated these and additional medical disciplines such as drug formulation, medicinal chemistry, drug toxicity, clinical practice guidelines, drug discovery and development, therapeutics, biostatistics, pharmacoeconomics, and clinical trial assessment and interpretation. This is evident through entries on my CV, which include over 100 peer-reviewed publications and hundreds of presentations on these topics.

4. Metabolism of Valsartan

a. The pharmacologic properties of valsartan have been thoroughly studied and therefore are well understood.

Valsartan has been in clinical use for more than three decades, and thousands of research studies ranging from in vitro pharmacology, animal pharmacology and toxicology, and human studies have been conducted on this drug. The following summarizes important features of valsartan, most of which have been known for decades.

As mentioned, valsartan is one of several drugs in the classification of angiotensin receptor blockers (ARBs). ARBs were a logical follow-up to the angiotensin converting enzyme inhibitors (ACEIs) which blocked the formation of angiotensin II, whereas ARBs block the effects of angiotensin II at its receptor, the AT_1 receptor. Angiotensin II (AII) is one of the most potent vasoconstrictors in humans and is implicated in the pathophysiology of hypertension, heart failure and certain types of kidney diseases. Thus, either blocking angiotensin II (AII) formation with an ACEI or its action at AT_1 receptors with an ARB improves patient outcomes in these important diseases. Although similar in benefit, ARBs are particularly important compared to ACEIs as they are much less likely to cause some of the ACEIs' more serious side effects, cough and angioedema. Angioedema is the more serious of the ACEI side effects and is an allergic type

reaction that manifests as swelling of the face, lips, tongue and sometimes the airway, which can lead to severe shortness of breath and may require the insertion of breathing tubes.

Therefore, ARBs including valsartan are frequently prescribed for patients who have experienced or are at higher risk for the ACEI related side effects in patients with these important cardiovascular and renal diseases. Any disruption in therapy for safety concerns, such as the presence of trace amounts of NDMA/NDEA or other nitrosamines, should be carefully considered in the context of the important clinical benefit the ARB is providing, as discussed more fully below. This balance of risk vs. benefit is the cornerstone of therapeutic decision-making.

b. Valsartan Pharmacokinetics

After oral administration in humans, valsartan is absorbed into the body primarily in the small intestine (below the level of the stomach) and reaches peak plasma concentrations between two and four hours. The amount of a given dose that reaches the systemic circulation (beyond the liver) is expressed by the term absolute bioavailability, and this ranges from 10-35%, averaging 25%.[9] This means that only ¼ of a valsartan dose, on average, actually circulates in the blood stream to reach the AT1 receptor sites, the valsartan mechanism of action. After absorption in the body, the first organ to see valsartan, the liver, uses CYP2C9 to metabolize only a very small amount, about 11%, producing an inactive metabolite.[10] Because of such a small amount of reliance on the CYP2C9 pathway, the potential for P450 based drug

[9] Flesch G, Müller P, Lloyd P, *Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man*, Eur. J. Clin. Pharmacol. 52(2):115-20 (1997).

[10] Nakashima A, Kawashita H, Masuda N, Saxer C, Niina M, Nagae Y, Iwasaki K, *Identification of cytochrome P450 forms involved in the 4-hydroxylation of valsartan, a potent and specific angiotensin II receptor antagonist, in human liver microsomes*, Xenobiotica 35(6):589-602 (2005).

interactions is negligible. About 80% of valsartan is excreted unchanged and found in the feces.[11] Most of this fecal elimination comes from biliary excretion from the liver. Thus, there is very little actual metabolism of valsartan, and no significant drug interactions involving valsartan ADME have been identified. The only identified drug interactions with valsartan are pharmacodynamics in nature, meaning that drugs might cause fluid retention (such as ibuprofen or other NSAIDs) that could offset the beneficial blood pressure effects, or drugs might cause an increase in serum potassium levels, seen with valsartan, an effect also seen with spironolactone.[12] With this pharmacokinetic and pharmacodynamics profile, nitrosamines like NDMA/NDEA would not alter the pharmacokinetics of or response to valsartan since there is no common pathway of metabolism or alteration of its metabolism or effect.

Although not metabolized, following absorption, valsartan is taken up by the liver through an uptake transporter protein called organic anion transporter polypeptide 1B1 (OATP1B1). OATP1B1 is not a metabolizing protein, but transports valsartan into the liver, the first step in its biliary excretion process outlined above. Following liver uptake, valsartan excretion into bile and subsequently the feces, is mediated by another non-metabolizing transporter protein, multi-drug resistant related protein 2, or MRP2. In theory, inhibitors of either of these eliminating transporters could increase valsartan systemic exposure, although specific drug interactions through these processes have not been specifically conducted. In fact, in one study in patients with a genetic reduction in OATP1B1 activity, there was little effect

[11] Waldmeier F, Flesch G, Müller P, Winkler T, Kriemler HP, Bühlmayer P, De Gasparo M, *Pharmacokinetics, disposition and biotransformation of [14C]-radiolabelled valsartan in healthy male volunteers after a single oral dose*, Xenobiotica 27(1):59-71 (1997).

[12] *See, e.g.*, Teva Valsartan package label (Rev. Dec. 2014).

on valsartan pharmacokinetics (blood levels), indicating that even if NDMA/NDEA altered this transporter protein (although never demonstrated), there would be no significant effect on valsartan drug levels or response.[13] In any event, there is no known or identified interaction with these transporters and NDMA/NDEA or other nitrosamines, so there is no known interaction of NDMA/NDEA with the hepatic uptake or biliary excretion of valsartan, and thus no know alteration in valsartan's clinical effects.

5. Generic Pharmaceutical Drug Approval by FDA

a. ANDA Process

The FDA has authority to approve generic drugs through its Abbreviated New Drug Application ("ANDA") process.[14] Generic drugs generally are the same in terms of active ingredient, dosage form, strength, route of administration, quality, performance characteristics, and labeling for any intended indications. Once these dosage form characteristics are demonstrated in the sponsor ANDA, the approved generic drug will be added alongside the innovator original branded drug and be listed in the *FDA's Approved Products with Therapeutic Equivalence Evaluations*, also known as the Orange Book. The submission process is termed abbreviated because the sponsor of a generic drug is generally not required to conduct and include additional preclinical (animal) or clinical (human) safety and efficacy trials, and is instead granted approval status based on the safety and efficacy data previously submitted by the drug innovator or NDA holder. However, the generic drug sponsor must demonstrate that their product will perform in the same manner as the innovator drug. The usual way for

[13] Maeda, *Effect of organic transporting polypeptide haplotype on pharmacokinetics of pravastatin, valsartan and temocapril*, Clin. Pharmacol. Ther. 79(5):427-439 (2006).
[14] *See generally* FDA.gov.

demonstrating performance in the same manner as the original product is to conduct bioequivalence studies. The generic drug sponsor will conduct these bioequivalence studies to show their product has the same rate and extent of bioavailability such that the same amount of **active ingredient** will be in a patient's blood stream in the same amount of time as that of the innovator drug.[15]

b. FDA-Approved ANDAs for Valsartan and Combination Products

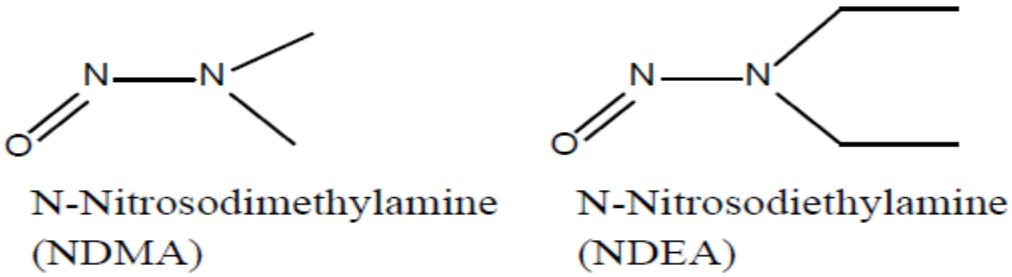
I have reviewed the FDA-approved ANDA data for Teva valsartan (40mg, 80mg, 160mg, 320mg), valsartan plus hydrochlorothiazide, valsartan plus amlodipine, and valsartan/amlodipine/hydrochlorothiazide. The FDA approval for these generic products was, in part, based on demonstrating that the intended, active ingredient(s) had bioavailability studies that fell well within the FDA parameters for meeting bioequivalence to the reference products Diovan, Diovan HCT, Exforge and Exforge HCT. It is my opinion that the presence of trace quantities of NDMA and NDEA would not alter the validity of these FDA approved generic equivalents, based on the complete lack of overlap in any of the pharmacokinetic processes of valsartan when compared to the metabolic fate of either NDMA or NDEA as described below.

6. Metabolism and Pharmacokinetics of NDMA and NDEA

NDMA (N-nitrosodimethylamine) and NDEA (N-nitrosodiethylamine) have the following chemical structures:

[15] I reserve the right to supplement this report to offer complete opinions regarding bioequivalence as it relates to class action claims, liability, specific causation, damages and/or other issues during subsequent phases of discovery.

Figure 4.[16]



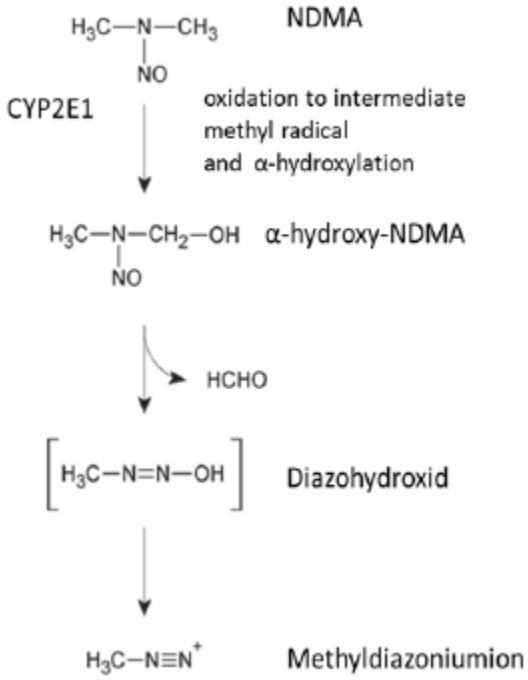
These two compounds and others are in a structural category called nitrosamines, and are produced in the drug manufacturing process by a chemical reaction between amines (a single nitrogen derivative of ammonia) and nitrous acid. The concern over the detection of these impurities is that the International Agency for Research on Cancer (IARC) has categorized nitrosamines as a probable human carcinogen based on animal studies, primarily involving rats.[17] Nitrosamines are unintentionally produced as a byproduct of industrial methods in the production of medications, tanneries, pesticides, rubber/tires and fish processing.[18] NDMA is also found in many foods, such as cured meats and cheeses, foods preserved by smoking (meat, fish), beer and pickled vegetables. Since only animal data are available on the relationship between dose of nitrosamines and cancer risk, we refer to animal data in assessing any correlation between the exposure to NDMA/NDEA in valsartan products and the estimated clinical impact, with an understanding of the limitations in its ability to reliably predict or establish causation in humans.

[16] *FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs* at 4, fig. 2 (Sept. 2020).
[17] WHO / IARC (International Agency for Research on Cancer World Health Organization), *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Some N-Nitroso Compounds* Vol. 17 (May 1978).
[18] EPA, *Technical Fact Sheet - N-Nitroso-dimethylamine* (NDMA) (2014).

a. Metabolic fate of NDMA/NDEA

There are two identified metabolic pathways for the metabolism of NDMA, seen below, which also apply to NDEA.

Figure 5.[19]



The alpha-hydroxylation pathway produces the methyldiazonium ion, which binds with a segment of DNA to produce the primary mutagenic and carcinogenic substance, O^6-methyl-guanine.[20] A key step in this metabolic activation to a potential carcinogen, is the hydroxylation of NDMA/NDEA by cytochrome P450 pathways—CYP2E1 is used almost exclusively for NDMA,

[19] EMA, *Assessment Report: Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group* 15 fig. 7 (2019).

[20] Liteplo RG et al. (WHO), *Concise International Chemical Assessment Document 38: N-nitrosodimethylamine January 2002 IPCS Concise International Chemical Assessment Documents* (2002).

and both CYP2E1 and CYP2A6 are used for NDEA.[21] The methyldiazonium ion is too unstable to escape from the cell in which it is generated, and therefore the carcinogenic potential would be limited to the organ both receiving the NDMA/NDEA and having the requisite CYPs able to produce it.[22] Thus, the carcinogenic potential will, in part, be determined by the distribution of NDMA/NDEA to tissues with the capacity to metabolize through the CYP2E1 and CYP2A6 pathways for NDMA and NDEA, respectively, and the delivery of the nitrosamines to that organ.

Due to a known high rate of first-pass metabolism, the pharmacokinetics of nitrosamines will depend on the route of administration. Following intravenous, inhalation or intraperitoneal administration (IP), nitrosamines "skip" first-pass metabolism. Therefore, as described above, if administered through these non-oral methods, none of which is at issue in this litigation, NDMA/NDEA would be expected to reach the systemic circulation and be delivered to the various tissues and organs receiving blood flow. Since the P450 metabolism step is key to producing the mutagenic metabolite of NDMA and NDEA, the amount of drug delivered and the individual metabolic capacity of that organ will determine how much carcinogen is produced.

However, following the principles of first-pass metabolism, orally administered NDMA and NDEA, such as the NDMA/NDEA present in valsartan, are absorbed through the upper small intestine with a half-life of absorption of three minutes and then directly circulated to the liver for metabolism.[23] The absorption process is described as first-order, meaning that absorption is

[21] Kushida H et al., *Metabolic activation of N-alkylnitrosamines in genetically engineered salmonella typhimurium expressing CYP2E1 or CYP2A6 together with human NADPH-cytochrome P450 reductase*, Carcinogenesis 21(6):1227-32 (2000); Bellec G. et al., *Cytochrome P450 Metabolic Dealkylation of Nine N-nitrosodialkylamines by Human Liver Microsomes*, Carcinogenesis 17(9):2029-2034 (1996).
[22] Pegg AE, *Metabolism of N-nitrosodimethylamine*, IARC Sci Publ. (27):3-22 (1980).
[23] *Id.*

not saturable.[24] Although many CYP enzymes are found in the gut wall and are able to metabolize prior to reaching the liver, neither CYP2E1 nor CYP2A6 are found in appreciable amounts in the gut wall; thus CYP-mediated metabolism of NDMA and NDEA following low dose oral administration would be isolated to the liver, until a dose was given that exceeded the first-pass capacity of the liver.[25] Furthermore, there have been no appreciable genetic polymorphisms identified in CYP2E1 that would result in loss of function such that the metabolic capacity of the liver could be "overloaded" and result in more widespread NDMA/NDEA distribution to organs beyond the liver.[26] Smaller oral doses are metabolized in the liver almost completely, minimizing exposure to other tissues and organs. Thus, metabolism of NDMA/NDEA that is ingested orally—such as the trace NDMA/NDEA found in orally ingested valsartan—is a classic example of first-pass metabolism: at low oral doses, like the trace amounts found in valsartan products, metabolism occurs almost entirely during the compound's first pass through the liver, before it ever reaches systemic circulation.

The localization of NDMA/NDEA metabolism to the liver in doses of valsartan is further supported by studies involving administration of nitrosamines in rats. However, because route of administration so greatly dictates the methods and nature of absorption, metabolism, and distribution, including in the case of NDMA's/NDEA's metabolic fate, as demonstrated above, studies involving non-oral administration of nitrosamines in rats are not relevant in considering

[24] Gomez M. I. D. et al., *The Absorption and Metabolism in Rats of Small Oral Doses of Dimethylnitrosamine*, Biochem. J. 164:497-500 (1977).
[25] Chen J, Jiang S, Wang J, Renukuntla J, Sirimulla S, Chen J, *A comprehensive review of cytochrome P450 2E1 for xenobiotic metabolism*, Drug Metab. Rev. 51(2):178-195 (2019); Tanner JA, Tyndale RF, *Variation in CYP2A6 Activity and Personalized Medicine*, J. Pers. Med. 1;7(4):18 (2017).
[26] Chen J, Jiang S, Wang J, Renukuntla J, Sirimulla S, Chen J, *A comprehensive review of cytochrome P450 2E1 for xenobiotic metabolism*, Drug Metab. Rev. 51(2):178-195 (2019).

the metabolic fate of NDMA/NDEA in orally ingested valsartan. Only studies involving oral doses of nitrosamines can provide the proper background with which to interpret and extrapolate the content of these nitrosamines in valsartan products.

b. NDMA and NDEA have an additive, and *not* a synergistic, effect.

It is a well-established principle of pharmacology that most, if not all, drugs will exhibit a dose-response relationship—i.e., the greater the amount of drug administered, the larger the biological response will be, until the target (e.g., enzyme, receptor) reaches its maximal response, such that additional doses/concentrations cannot illicit any additional response. It is equally accepted that two drugs that individually produce the same biological effect may have a greater effect when they are used together. This occurs even when the molecular mechanism of action differs between the drugs. Pharmacologists recognize different types of drug combinations effects: two drugs can be *additive* in their actions (1 + 1 = 2), or they can be *synergistic* in their actions (1 + 1 = 3)

I disagree with Dr. Lagana's suggestion of "synergy" between NDMA and NDEA if given in trace amounts in valsartan generic products. When drugs are given together or in sequence, it is not possible to distinguish which drug is responsible for the observed response, or which agent caused any particular adverse effects or toxicities. NDEA and NDMA share a somewhat common P450 pathway, 2E1; however, the metabolism of NDEA is more closely associated with 2A6. This suggests that NDMA and NDEA will be metabolized independently and do not alter the metabolism of each other. As a result, the presence of both NDMA and NDEA in valsartan would create an additive, and not a synergistic, effect.

7. NDMA/NDEA are not proven to cause cancer in humans.

a. Carcinogenesis requires activation by 2E1-based metabolism.

The presence of NDMA or NDEA in the bloodstream alone does not make NDMA/NDEA carcinogenic. Rather, for carcinogenesis, NDMA/NDEA must be activated to the carcinogen by CYP2E1-based metabolism. Specifically, for NDMA/NDEA to become a carcinogen, it requires metabolism in the organ that will ultimately be affected, since the NDMA/NDEA metabolic product that is carcinogenic is considered unstable and therefore unable to be released to the blood stream or to reach tissues other than those in which it was generated.[27] Therefore, for NDMA/NDEA to be carcinogenic in a particular organ, it requires two specific criteria to be met: 1) the delivery of NDMA/NDEA to that organ either directly by inhalation/injection or indirectly by an oral dose exceeding hepatic clearance and then reaching the systemic circulation; and 2) the organ having the capacity to metabolize the nitrosamine to its corresponding carcinogen through the respective CYP450 pathway.

Accordingly, when evaluating literature for nitrosamine exposure, and comparing it to the issues at hand (i.e., exposure to NDMA/NDEA in valsartan), inhaled, injected (IV or IP) or large oral doses of nitrosamine are not comparable to the small oral doses of NDMA and NDEA found in valsartan products. Therefore, for many of the studies relied upon by Plaintiffs' experts, the dose used in the studies and routes of administration do not provide a reliable basis for reaching any conclusions as to dose or method of exposure in humans.

[27] Pegg AE, *Metabolism of N-nitrosodimethylamine*, IARC Sci Publ. (27):3-22 (1980).

b. Animal studies do not support an independent or increased risk of cancer from exposure to NDMA/NDEA in valsartan, at the levels and for the time period at issue in this litigation.

i. *Ito Study*[28]

Ito studied the impact of various nitrosamines on rats, which included a long-term study of male and female rats administered an NDMA-containing diet for 96 weeks. Ito found that chronic (96 weeks) NDMA exposure at a dose of 10mg/kg/day was associated with liver tumors in rats; however, a dramatically reduced number of liver cancers were seen at the dose of 1.0 mg/kg, and a dose of 0.1 mg/kg/day showed no increase in liver tumor occurrence. No tumors were observed in other organs even at the higher dose. This demonstrates that doses of NDMA as high as 10mg/kg/day are efficiently eliminated by the liver, resulting in no systemic exposure to other tissues and organs. Two major conclusions were drawn by Ito:

- The minimum carcinogenic intake of NDMA through an oral route is 1.0mg/kg; and
- The non-effective level of carcinogenesis was 0.1mg/kg by the oral route.

As 0.1 mg/kg corresponds to a daily dose of 7mg of NDMA in a typical size adult of 70kg, this non-carcinogenic dose would correspond to a daily dose over 300 times higher than the highest amount of NDMA found in any valsartan product. Stated another way, the highest amount of NDMA in a valsartan product is only 0.03% of the non-carcinogenic dose from the Ito study. Below is a similar comparison of the non-carcinogenic dose of NDMA in the Ito study (0.1mg/kg) and how this compares to the amount of NDMA found in valsartan products

[28] Ito N et al., *Induction of preneoplastic and neoplastic lesions in rats treated N-nitroso compounds*, N-Nitroso Compounds: Occurrence and Biological Effects (41):597-601 (1982).

557 manufactured by various generic manufacturers of finished dose products which were analyzed

558 by the FDA:

559 *Ratio of Ito daily non-carcinogen dose of NDMA (0.1mg/kg or 7mg in a typical human adult) to*
560 *daily NDMA ingested in various valsartan generic products.*

Company	**Product**	**NDMA Range (mcg)**	**NDEA Range (mcg)**	**Estimated Daily Human NDMA Exposure**	**Estimated NDEA Exposure**	**Ratio to Valsartan Amount (NDMA)**	**Ratio to Valsartan Amount (NDEA)**
Aurobindo Pharm LTD	Amlodipine 10mg, valsartan 320mg	Below LOD	0.02-0.09	7mg (70000 mcg)	--	--	--
Aurobindo Pharm LTD	Valsartan 320mg	Below LOD	0-0.05	7mg (70000 mcg)	--	--	--
Aurobindo Pharm LTD	Valsartan 320mg, HCTZ 25mg	Below LOD	0.02-0.19	7mg (70000 mcg)	--	--	--
Hetero Labs LTD	Valsartan 320mg	0.33-0.44	Below LOD	7mg (70000 mcg)	--	15,909-21,212x	--
Mylan Pharmaceutical Inc	Amlodipine 10mg, valsartan 320mg	Below LOD	0.04-0.11	7mg (70000 mcg)	--	--	--
Mylan Pharmaceutical Inc	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	Below LOD	0.05	7mg (70000 mcg)	--	--	--
Mylan Pharmaceutical Inc	Valsartan 320mg	Below LOD	0.07-0.16	7mg (70000 mcg)	--	--	--
Mylan Pharmaceutical Inc	Valsartan 320mg, HCTZ 25mg	Below LOD	0.2-0.38	7mg (70000 mcg)	--	--	--
Prinston Pharmaceutical	Valsartan 320mg	15.18-16.30	Below LOD	7mg (70000 mcg)	--	429-461x	--
Prinston Pharmaceutical	Valsartan 320mg, HCTZ 25mg	13.18-20.19	Below LOD	7mg (70000 mcg)	--	347-531x	--
Teva Pharmaceutical	Amlodipine 10mg, valsartan 320mg	Below LOD	0-0.03	7mg (70000 mcg)	--	--	--
Teva Pharmaceutical	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	Below LOD	0-0.03	7mg (70000 mcg)	--	--	--

Teva Pharmaceutical	Valsartan 320mg	7.92-16.55	Below LOD	7mg (70000 mcg)	--	423-884x	--
Teva Pharmaceutical	Valsartan 320mg, HCTZ 25mg	6.94-10.35	0-0.77	7mg (70000 mcg)	--	676-1009x	--
Torrent Pharmaceuticals	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	10.24-11.53	Below LOD	7mg (70000 mcg)	--	--	--
Torrent Pharmaceuticals	Valsartan 320mg	0.56-0.62	1.12-1.22	7mg (70000 mcg)	--	11,290-12,500x	--
Torrent Pharmaceuticals	Valsartan 160mg	0.45	1.31	7mg (70000 mcg)	--	15,556x	--

ii. *Pegg Paper*[29]

The Ito study results mirror those reported by Pegg, who studied the uptake and metabolism of NDMA. Pegg's research showed that the ratio of hepatic to kidney carcinogen production with **IV** administration of NDMA is approximately 8:1 across a wide dose range of between 1 mcg/kg to 100 mcg/kg. This reflects an approximation of the ratio of CYP metabolic activity between the two organs, with the liver having higher CYP activity than the kidney by a similar ratio. However, when NDMA is given **orally** over the same dosage range, the ratio of carcinogen production ranges from 33-52:1 (liver to kidney), reflecting "localization" of metabolism in the liver following oral doses. Further, doses as low as 0.1 and 1.0mg/kg/day do not appear to exceed the capacity of the liver to metabolize the potential carcinogen. This may be due to the presence in the liver of a carcinogenic "surveillance" system that removes O^6-methyl-guanine from DNA prior to carcinogenesis. Therefore, with the low level exposure of NDMA/NDEA in the valsartan generic products, the production of potential carcinogen is within the organ with the highest capacity for its removal.

[29] Pegg A.E., *Metabolism of N-Nitrosodimethylamine*, Molecular and Cellular Aspects of Carcinogen Screening Tests 3–22 (1980).

iii. *Peto Study*[30]

In one of the largest rat studies across a broad range of doses, Peto studied 4,080 rats administered various levels of NDMA/NDEA in drinking water, for a period of either 12 or 18 months. Peto published two studies based on this same experiment: one was on the dose-response relationship between either NDMA and NDEA and cancer formation (including death) and the other was on the dose-time relationship.

One significant finding was that at NDEA doses below or equal to 0.264 parts per million (ppm) given orally, an approximate dose of 13.2 mcg/kg and below, there were no esophageal pre-cancerous tumors, cancerous tumors or esophageal cancer deaths. This is consistent with lower oral doses of NDEA being confined to the liver and not exceeding hepatic metabolic capacity. Further, this upper dose of 13.2 mcg/kg would correspond to a daily dose of 924 mcg of NDEA in an adult, or more than 700 times the largest amount of NDEA found in any generic valsartan product, making the NDEA exposure unlikely to cause any cancer by "escaping" first-pass metabolism.

In the Peto study, the relationship between the oral dose of either NDMA or NDEA and liver cancer was complicated by the observation that 8% of the control treated rats still developed hepatic cancers. When looking at the dose of NDMA associated with an observed lifetime hepatic cancer rate above the "background" hepatic cancer rate with no treatment, an apparent increase in liver cancer was only seen at doses above 0.3 ppm, equating to 15

[30] Peto R et al., *Effects on 4080 Rats of Chronic Ingestion of Nitrosodiethylamine or N-Nitrosodimethylamine: A detailed dose response study*, Cancer Research 51:6415-6451 (1991) ("Peto 1991a"); Peto R et al., *Dose and Time Relationships for Tumor Induction in the Liver and Esophagus of 4080 Inbred Rats by Chronic Ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine*, Cancer Research 51:6452-6469 (1991) ("Peto 1991b").

mcg/kg/day. This would approximate an adult dose of 1050 mcg/day, or more than 52 times the highest NDMA amount found in any generic valsartan product, keeping in mind that the potential human exposure with valsartan containing NDMA would be less than lifetime (6 years or less vs. lifetime in the rat study). As above, I have calculated the ratio of Peto daily doses for NDMA and NDEA vs the amounts of both compounds found in the FDA analysis of valsartan generic products:

Ratio of Peto daily non-carcinogen dose of NDMA (15 mcg/kg/day or 1050 mcg/day in a typical human adult) or NDEA (13.2 mcg/kg or 924mcg/day) to daily NDMA and NDEA ingested in various valsartan generic products.

Company	Product	NDMA Range (mcg)	NDEA Range (mcg)	Estimated Daily Human NDMA Exposure	Estimated NDEA Exposure	Ratio to Valsartan Amount (NDMA)	Ratio to Valsartan Amount (NDEA)
Aurobindo Pharm LTD	Amlodipine 10mg, valsartan 320mg	Below LOD	0.02-0.09	1050mcg	924mcg	--	10,267-46,200x
Aurobindo Pharm LTD	Valsartan 320mg	Below LOD	0-0.05	1050mcg	924mcg	--	18,480x
Aurobindo Pharm LTD	Valsartan 320mg, HCTZ 25mg	Below LOD	0.02-0.19	1050mcg	924mcg	--	4,863-46,200x
Hetero Labs LTD	Valsartan 320mg	0.33-0.44	Below LOD	1050mcg	924mcg	2,386-3,182x	--
Mylan Pharmaceutical Inc	Amlodipine 10mg, valsartan 320mg	Below LOD	0.04-0.11	1050mcg	924mcg	--	8,400-23,100x
Mylan Pharmaceutical Inc	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	Below LOD	0.05	1050mcg	924mcg	--	18,480x
Mylan Pharmaceutical Inc	Valsartan 320mg	Below LOD	0.07-0.16	1050mcg	924mcg	--	5,775-13,200x
Mylan Pharmaceutical Inc	Valsartan 320mg, HCTZ 25mg	Below LOD	0.2-0.38	1050mcg	924mcg	--	2,432-4,620x
Prinston Pharmaceutical	Valsartan 320mg	15.18-16.30	Below LOD	1050mcg	924mcg	64-69x	--

Prinston Pharmaceutical	Valsartan 320mg, HCTZ 25mg	13.18-20.19	Below LOD	1050mcg	924mcg	52-80x	--
Teva Pharmaceutical	Amlodipine 10mg, valsartan 320mg	Below LOD	0-0.03	1050mcg	924mcg	--	30,800x
Teva Pharmaceutical	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	Below LOD	0-0.03	1050mcg	924mcg	--	30,800x
Teva Pharmaceutical	Valsartan 320mg	7.92-16.55	Below LOD	1050mcg	924mcg	63-133x	--
Teva Pharmaceutical	Valsartan 320mg, HCTZ 25mg	6.94-10.35	0-0.77	1050mcg	924mcg	101-151x	1200x
Torrent Pharmaceuticals	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	10.24-11.53	Below LOD	1050mcg	924mcg	91-103x	--
Torrent Pharmaceuticals	Valsartan 320mg	0.56-0.62	1.12-1.22	1050mcg	924mcg	1,694-1,875x	757-825x
Torrent Pharmaceuticals	Valsartan 160mg	0.45	1.31	1050mcg	924mcg	2,333x	705x

603 I should note that in the very complicated Peto papers, the statistics, mathematical
604 projections and calculations of probabilities and trends are quite complex. One quote taken
605 from one of the Peto papers and used by several of Plaintiffs' experts, is that there is a 25%
606 excess of liver cancer at a dose of 1ppm, 2.5% at 0.1ppm, and therefore 0.25% at 0.01ppm, with
607 no apparent threshold.[31] However, from the remainder of that paragraph, in Peto's conclusion,
608 is the comment that "the general arguments about the ***likely*** shapes of dose-response
609 relationships make it probable, even at lower doses, where direct observation is impracticable,
610 this linear relationship ***may*** remain approximately true, for Colworth rats, if not for humans."
611 The basis for this "trend" analysis is from pooling the NDMA and NDEA treatment groups, both

[31] Peto 1991a.

male and female, and performing the trend statistics on these data. The trend analysis of the pooled data are presented in table 28 from Peto's 1991a paper. However, when looking at the trend statistics in the table legend, the critical z value is 2.16. In the methodology section of the same paper, the trend statistics description states: "[I]f the IP (one tailed P value) is of intermediate value (eg. when 2<z<3), then judgment as to how likely it is that treatment really did cause the disease of interest becomes more difficult…." Thus, the reliability of using a linear dose response relationship for liver cancer at low doses of NDMA and NDEA is not well established, contrary to the representations of Plaintiffs' experts. Peto goes on to say that decisions would need to be more based on biological than statistical results, meaning that observed liver cancers become more important than calculated ones. Thus, the number of liver cancers seen between the control groups and NDEA/NDMA doses of up to 0.066 ppm (3.3 mcg/kg) were the same, making it impossible to biologically conclude that these doses cause liver cancer. The 3.3 mcg/kg dose corresponds to a human daily dose of 231 mcg, still almost 11 times the dose of NDMA in any generic valsartan product (with the additional difference in lifetime rat exposure vs. less than lifetime, 6 years or less, in humans).

iv. *Brantom Study*[32]

An additional study on the dose-response relationship between nitrosamines and cancer in rats is seen in a graduate thesis paper by Brantom in 1983. In his introductory remarks, Brantom considers "the possibility that at very low levels of exposure there is no effect." In his thesis study, Brantom chose water-based NDMA and NDEA doses administered to rats in the

[32] Brantom P.G., *Dose-Response Relationships in Nitrosamine Carcinogenesis*, The British Industrial Biological Research Association (BIBRA) (1983).

dose range of 33 – 16,896 parts per billion (ppb), identical to the dose range in the previously mentioned Peto study. (This is not surprising in that Dr. Brantom is also an author on the Peto papers.) Thus, the same conversion of the ppb to dose/kg gives a dose range of approximately 2-1470 mcg/kg/day, as reflected in Brantom's Table 4.1. Doses of NDEA below about 80 mcg/kg/day and NDMA below about 120 mcg/kg/day had mortality rates no different from the control group in Brantom's study. Roughly 80-95% of control rats had tumors upon death, again emphasizing that there is background "noise" for tumor studies in rats. From Tables 4.6-4.9 in Brantom's paper, one can see that liver tumors did not occur with NDEA or NDMA in what could be called a dose-response relationship, and above what is seen in control rats, until a dose of 132 ppb or higher for male and female rats, corresponding to a dose of approximately 8-11 mcg/kg/day. This would correspond to a human daily dose of approximately 700 mcg/day, or 35 times higher than the highest amount of NDMA found in any generic valsartan product and 530 times higher than the highest amount of NDEA found in any generic valsartan product. As above, I have calculated the ratio of the non-cancerous doses of both NDMA and NDEA in the Brantom study with the various daily amounts of both found in valsartan generic products:

Ratio of Brantom daily NDMA and NDEA ingestion (700 mcg/day) not associated with cancers to the amount for both found in valsartan generic products.

Company	Product	NDMA Range (mcg)	NDEA Range (mcg)	Estimated Daily Human NDMA Exposure	Estimated NDEA Exposure	Ratio to Valsartan Amount (NDMA)	Ratio to Valsartan Amount (NDEA)
Aurobindo Pharm LTD	Amlodipine 10mg, valsartan 320mg	Below LOD	0.02-0.09	700mcg	700mcg	--	7,778-35,000x
Aurobindo Pharm LTD	Valsartan 320mg	Below LOD	0-0.05	700mcg	700mcg	--	14,000x

Aurobindo Pharm LTD	Valsartan 320mg, HCTZ 25mg	Below LOD	0.02-0.19	700mcg	700mcg	--	3,684-35,000x
Hetero Labs LTD	Valsartan 320mg	0.33-0.44	Below LOD	700mcg	700mcg	1,591-2,121x	--
Mylan Pharmaceutical Inc	Amlodipine 10mg, valsartan 320mg	Below LOD	0.04-0.11	700mcg	700mcg	--	6,364-17,500x
Mylan Pharmaceutical Inc	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	Below LOD	0.05	700mcg	700mcg	--	14,000x
Mylan Pharmaceutical Inc	Valsartan 320mg	Below LOD	0.07-0.16	700mcg	700mcg	--	4,375-10,000x
Mylan Pharmaceutical Inc	Valsartan 320mg, HCTZ 25mg	Below LOD	0.2-0.38	700mcg	700mcg	--	1,842-3,500x
Prinston Pharmaceutical	Valsartan 320mg	15.18-16.30	Below LOD	700mcg	700mcg	43-46x	--
Prinston Pharmaceutical	Valsartan 320mg, HCTZ 25mg	13.18-20.19	Below LOD	700mcg	700mcg	34.7-53.1x	--
Teva Pharmaceutical	Amlodipine 10mg, valsartan 320mg	Below LOD	0-0.03	700mcg	700mcg	--	23,333x
Teva Pharmaceutical	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	Below LOD	0-0.03	700mcg	700mcg	--	23,333x
Teva Pharmaceutical	Valsartan 320mg	7.92-16.55	Below LOD	700mcg	700mcg	42.3-88.4x	--
Teva Pharmaceutical	Valsartan 320mg, HCTZ 25mg	6.94-10.35	0-0.77	700mcg	700mcg	67.6-100.9x	909x
Torrent Pharmaceuticals	Amlodipine 10mg, valsartan 320mg, HCTZ 25mg	10.24-11.53	Below LOD	700mcg	700mcg	60.7-68.4x	--
Torrent Pharmaceuticals	Valsartan 320mg	0.56-0.62	1.12-1.22	700mcg	700mcg	1,129-1,250x	573.8-625x
Torrent Pharmaceuticals	Valsartan 160mg	0.45	1.31	700mcg	700mcg	1555x	534x

649 Similarly, the occurrence of esophageal cancers was only dose-response evident, and

650 only in males at NDEA doses above 1580 ppb, or approximately 100 mcg/kg/day. This would

correspond to a daily human dose approximately 5343 times higher than the dose of NDEA found in any generic valsartan product. Further, in scanning the other cancers observed in all rats, at all doses, both male and female, there was no evident dose-response relationship with either NDEA or NDMA.

A further analysis showed all treatment-related tumors in Tables 4.14 and 4.15 only occurred with clear frequency above control rats at an NDEA dose above 1060 ppb (about 80 mcg/kg/day). Brantom states a similar pattern existed for NDMA. He further states that doses below 200 mcg/kg/day revealed a reduction in tumor incidence in a dose-related fashion, but does not state that it was linear.

With the observance of few cancers observed at low doses, and not different from control animals, Brantom states that "any calculation of effect is based on extrapolation," indicating the potential inaccuracy of assuming there is no "threshold" effect—that is, a dose below which neither NDMA nor NDEA causes cancer. Given the assumptions in extrapolating animal data to humans, Brantom nevertheless made calculations of the median time to tumor occurrence in days for humans with higher nitrosamine doses (100 mcg per day) vs. lower doses (10 mcg per day). A final conclusion reached by Brantom is that based on his projections, extrapolations and assumptions, in the United Kingdom human population, exposure of 100 mcg per day to NDMA is unlikely to increase human death rate by any detectable amount.

v. *Terracini Study*[33]

Terracini attempted to find a non-effective dose of NDMA in rats. NDMA was administered in doses of 2-50 ppm in the diet by adding NDMA in an oil solution to the diet. Doses below 20 ppm did not induce liver histologic changes any different from untreated rats. Although some hepatic cysts were seen at the dose of 5ppm, only one hepatic tumor was seen at a dose of 2ppm. However, the number of rats receiving no NDMA was too small to ascertain the background number of liver tumors, so no correction for background noise was made. No kidney tumors were seen. The authors concluded that there was no obvious relationship between the site and frequency of tumors and the dose of NDMA. Further, they concluded that there was no "precancerous" histological or cytological that would provide possible evidence of impending malignancy.

vi. *Nixon Study*[34]

Nixon studied the combined effects of NDEA with cyclopropenoid fatty acids and aflatoxin in rats. The NDEA was administered in the drinking water. Along with the other compounds, NDEA was given in two doses, 0.2mg/kg/day and 1.0mg/kg/day. Both NDEA doses were associated with tumor formation; however, these doses are more than 10,000 and 53,000 times the daily amount of NDEA found in any NDEA-containing valsartan product.

[33] Terracini B et al., *Hepatic pathology in rats on low dietary levels of dimethylnitrosamine*, British Journal of Cancer 21:559-565 (1967).

[34] Nixon JE et al., *Effect of cyclopropenoid compounds on the carcinogenic activity of diethylnitrosamine and aflatoxin B in rats*, Journal of the National Cancer Institute 53:453-458 (1974).

vii. *Kroes Study*[35]

A study by Kroes compared, in rats, tumor rates with arsenic-based compounds alone and in combination with 25 mcg/week of NDEA (approximately 3.6 mcg/day), administered by esophageal intubation (not gastric). Over time, the rats gained weight such that the typical male weighed around 300 grams and a typical female around 175 grams. Thus, the dosing was approximately 12 mcg/kg/day for males and about 20mcg/kg/day for females. This corresponds to between 840-1400 mcg per day of NDEA, or more than 640-1069 times the highest amount of NDEA found in any valsartan product. Their results, even at this high-dose equivalent to humans for NDEA, revealed no indication that NDEA was able to induce tumors or potentiate the tumor effects of the arsenic compounds. Further, the authors concluded that there is a no-effect level for NDEA (again, at a dose of at least 640 times the amount of NDEA in any valsartan product).

viii. *Terao Study*[36]

Terao studied the combined effects of NDMA and sterigmatocystin on carcinogenesis in rats. NDMA was administered in the diet at doses of 1-10 ppm for 54 weeks. The livers of rats treated with 10ppm NDMA for 54 weeks showed almost normal histologic patterns and induced no hepatic carcinomas. There did seem to be an additive effect when NDMA was given with sterigmatocystin; however, that is not relevant to the valsartan context as sterigmatocystin is not found in or administered with valsartan.

[35] Kroes R et al., *Study on the carcinogenicity of lead arsenate and sodium arsenate and on the possible synergistic effect of diethylnitrosamine*, Food and Cosmetics Toxicology 12:671-679 (1974).
[36] Terao K et al., *A synergistic effect of nitrosodimethylamine on sterigmatocystin carcinogenesis in rats*, Food and Cosmetics Toxicology 16:591-596 (1978).

ix. *Arai Study*[37]

The Arai study is relied upon by Dr. Panigrahy to suggest there is evidence for low dose NDMA to cause many cancer types. Arai studied the lowest non-carcinogenic dose of NDMA in rats given 0.1, 1.0 and 10 ppm for 96 weeks. NDMA was added to the diet, presumably in the chow. No tumors were seen at the lowest dose of 0.1ppm, which translates into 0.35 mg/kg, or about 24mg per day in a human adult—over 1200 times the daily amount of NDMA found in any generic valsartan product. Of note, there were no renal tumors, and the authors conclude that to see renal carcinogenicity, higher doses of NDMA must be given by intraperitoneal injection, a route that would bypass first-pass metabolism. Thus, the Arai study does not support the induction of tumors with low dose NDMA with the trace amounts found in generic valsartan products, and does not support the opinions of Dr. Panigrahy on this issue.

x. *Angsubhakorn Study*[38]

In this study, Angsubhakorn observed the combined effects on rats of administering NDMA with aflatoxin, a potent hepatic carcinogen derived from fungal sources. Both chemicals were added to chow, with NDMA at a dose of 25 ppm. The lowest rate of carcinogenesis was with NDMA administered alone. Using a conversion from other rat studies, this dose of NDMA would equate to roughly 0.25mg/kg in rats, or 17.5mg per day, which is approximately 867 times the highest amount of NDMA in any valsartan product.

[37] Arai M et al., *Long-term experiment of maximal non-carcinogenic dose of dimethylnitrosamine for carcinogenesis in rats*, Japanese Journal of Cancer Research 70:549-558 (1979).
[38] Angsubhakorn S et al., *Enhancing effects of dimethylnitrosamine on aflatoxin B1 hepatocarcinogenesis in rats,* International Journal of Cancer 28:621-626 (1981).

xi. *Gricute Study*[39]

Griciute studied the impact of co-administering in mice NDMA with ethanol (40%, or 80 proof). The NDMA was administered by an intragastric tube at a weekly dose of 0.03mg for 50 weeks. Weights of the mice were not reported; however, in looking at the mice strain for research purposes at the Jackson Laboratory, the weight per mouse would appear to be somewhat age dependent, with a rough estimate of 25 grams (0.025kg) at about 12 weeks of age. Thus, I estimate the 0.03mg dose to be equivalent to 0.17 mg/kg/day (0.03mg/week x 1week/7 days x 1/0.025kg). This would correspond to a human adult dose of approximately 12mg per day, or approximately 700 times the amount of NDMA found in any Teva valsartan product.

xii. *Lijinsky Studies*

In 1981, Lijinsky conducted a dose response study of NDEA in rats, with total oral doses of 1.4 to 192mg in their drinking water for up to 30 weeks, then followed for up to 130 weeks.[40] The survival times were similar with total doses of 1.4-8.4mg and placebo. More cancers were seen in the higher doses and tended to be esophageal and hepatic. Animal size was not reported, making it difficult to convert to a human dose equivalent; however, if one estimates the weight of similar strain rats (300 gms or 0.3kg) and the 30 weeks of exposure, then the total administered lowest dose of 1.4 mg can be estimated as approximately 22 mcg/kg/day, or roughly 1540 mcg per day. This is over 1175 times the highest NDEA amount found in any

[39] Gricute L et al., *Influence of ethyl alcohol on carcinogenesis with Nnitrosodimethylamine*, Cancer Letters 13:345-352 (1981).
[40] Lijinsky W et al., *Dose response studies of carcinogenesis in rats by nitrosodiethylamine*, Cancer Research 41:4997-5003 (1981).

valsartan product, thus making it difficult to extrapolate these results to humans in the context of the microgram NDEA quantities found in valsartan.

In another study by Lijinsky in 1983, various combinations of n-nitrosoamines were given to rats to study the additive or synergistic effect of carcinogen combinations.[41] There was no clear indication of additive or synergistic effects with NDEA and other n-nitroso compounds with up to 30 weeks of individual or combination treatments. NDMA was not studied in this experiment.

In another Lijinsky study in 1984, NDMA was studied for effects on liver cancer in rats who also received other nitrosomethylalklyamines.[42] NDEA was not studied. The nitrosoamines were administered in drinking water, in total doses of 17 mg and 39 mg of NDMA. When 17 mg and 39 mg of NDMA given over 30 weeks are converted to human dose equivalents, one must again extrapolate the estimate weight of the rats used in the study.[43] At an estimate weight of 0.3kg, then the estimated dose of NDMA administered to these rats was between 270 and 540 mcg/day or approximately 19 mg and 38 mg per day. This translates into at least 941 and 1882 times the highest daily amount of NDMA found in any valsartan product.

In yet another Lijinsky study in 1987, a combination of NDMA and NDEA was administered to the same strain of Fischer rats with azoxyalkanes, also a known carcinogen.[44] The route of administration for NDMA and NDEA in this study was gastric lavage, a direct

[41] Lijinsky W et al., *Carcinogenesis by combinations of N-nitroso compounds in rats*, Food and Chemical Toxicology 21:601-605 (1983).
[42] Lijinsky W et al., *Carcinogenesis in rats by nitrosodimethylamine and other nitrosomethylalkylamines at low doses*, Cancer Letters 22:83-88 (1984).
[43] *See Fischer 344 rats,* taconic.com, https://www.taconic.com/rat-model/fischer-344 (last visited Aug. 2, 2021).
[44] Lijinsky W et al., *Carcinogenesis by nitrosodialkylamines and azoxyalkanes given by gavage to rats and hamsters*, Cancer Research 47:3968-3972 (1987).

administration technique compared to studies using drinking water. Interestingly, this author concedes in his introduction that it has "not been entirely appropriate to compare the biochemical results of carcinogenesis studies with the compound in drinking water" with studies using a more direct intragastric approach. This is presumed to be because in drinking water, animals get exposed through the skin, sublingual absorption and possibly inhalation—all of which are routes that circumvent the first-pass metabolism of compounds truly administered orally, thus confounding study results that use n-nitrosoamines in drinking water. Rats and hamsters were studied, but given the preponderance of rat studies, only the rat data are shown here. NDMA was administered in a dose of 1.9 mg/kg/day, and NDEA was administered in a dose of 2.3 mg/kg/day. Again, these are over 6587 times and 122,000 times the amount of daily exposure to these respective agents in any valsartan product. At these extreme doses, no esophageal cancers were seen with NDMA, and neoplasms of the nasal mucosa were uncommon with both NDEA and NDMA. Fewer liver tumors were seen with gavage than with drinking water studies of NDMA. NDEA induced tumors of the esophagus and nasal mucosa at these gavage doses.

xiii. *Adamson Study*[45]

Adamson reported an ongoing series of the carcinogenic effect of many compounds in non-human primates. None of four animals at necropsy had any cancer after receiving 10mg/kg biweekly intraperitoneal (IP) injections of NDMA, although there was evidence of hepatic toxicity (cirrhosis). Hepatocellular carcinomas were detected in monkeys receiving

[45] Adamson RH, *Chemical carcino-genesis in non-human primates. In:Longenbach R, Nesnow S, Rice JM, eds. Organand Species Specifcity in Chemical Carcinogene-sis*, New York and London: Plenum Publishing Corp. 129–156 (1983).

either bimonthly IP injections or 5 days/week oral doses of 40mg/kg of NDEA. This cumulative NDEA oral dose ranged in total from 18-55 grams, or 6274 to 19,170 times the total 6-year dose of the highest amount of NDEA in any valsartan product.

Adamson is also studying chronic doses of NDEA with IP doses of 0.1-40mg per kilogram. Given IP, these results are not relevant to low oral doses of NDEA.[46]

xiv. *Anderson Study*[47]

Anderson studied the effects on carcinogenesis of combining NDMA and ethanol in mice. The hypothesis is that ethanol, in part, is also metabolized by CYP2E1 (the major detoxifying metabolic pathway for NDMA), and that some studies suggest inhibition of 2E1 by ethanol. The dose of NDMA in this study was either 1 or 5 ppm and was administered to mice in drinking water. Although the addition of different amounts of ethanol appeared to increase the observance of lung tumors, many of the comparisons were not statistically significant. Further, 1mg/kg and 5mg/kg single NDMA doses were given directly into the stomach (intragastric, or IG) with and without ethanol. Although the 5mg/kg dose produced lung tumors in 16 weeks, the lung cancer rate with the 1mg/kg NDMA dose was no different than giving ethanol alone or the combination, until the highest ethanol dose was given. Thus the lower doses of NDMA seemed unaffected by any but the highest amount of ethanol, which would amount to consuming 40 proof alcohol in daily drinking water.

[46] Adamson et al., *The finding of n-nitrosodimethylamine in common medicines*, The Oncologist 25:460-462 (2020).
[47] Anderson LM et al., *Characterization of ethanol's enhancement of tumorigenesis by N-nitrosodimethylamine in mice*, Carcinogenesis 13:2107-2111 (1992).

xv. *Berger Study*[48]

Berger administered NDEA in the drinking water of rats who also received other carcinogens, to study the combination effects. Pertinent to the issues at hand, NDEA alone was administered in drinking water, 5 days a week, at doses of 0.01, 0.032 and 0.1 mg/kg. This would correspond to human adult doses of 0.7, 2.24 and 7mg per day—or 534-5344 times the highest daily amount of NDEA found in any valsartan product. Thus, the tumor rates in this study are not relevant in the context of human consumption of valsartan.

To a reasonable degree of scientific certainty, I can conclude from the above animal studies that most studies used doses of NDMA and NDEA that are far above, in some cases thousands of times above, the trace amounts of NDMA/NDEA found in valsartan products. I can also conclude that at the lower levels of oral exposure, the rates of measurable cancers were small and often no different from control animals' rates—the so-called "background noise." Because of the small rates at the lowest doses of NDMA and/or NDEA, the cancer rates are often extrapolated, which makes linearity assumptions that have not been proven. Therefore, I do not find evidence from the animal studies that the exposure to trace amounts of NDEA and/or NDMA in valsartan would be expected to lead to any detectable cancers.

c. The studies cited by Plaintiffs' experts also do not support any causal association between NDMA/NDEA in valsartan and the cancers alleged by Plaintiffs.

Throughout their reports, Drs. Panigrahy and Etminan rely on occupational studies involving NDMA exposure due to inhalation (e.g., exposure in rubber manufacturing workers) as well as animal studies involving NDMA exposure through injection. These studies are equally

[48] Berger MR et al., *Combination experiments with very low doses of three genotoxic N-nitrosamines with similar organotropic carcinogenicity in rats*, Carcinogenesis 8:1635-1643 (1987).

not relevant to the issues in this case, which involve the oral intake of small doses of NDMA, as the nature and mechanisms of absorption, distribution, and metabolism of NDMA are dependent upon the route of administration, as demonstrated above. And, in the studies of rubber manufacturing workers, there were several potential alternative sources of exposure to carcinogens that were not adequately controlled for, which is of particular importance given the various chemicals involved in the manufacturing process and the environment of a manufacturing plant. Specific criticisms of the studies relied upon by Plaintiffs' experts are set forth below.

i. *Occupational/Industrial Exposure*

Studies cited by Plaintiffs' experts include the following:

Study	Cancer Odds Ratio	Confidence Limits	Comments/Criticisms
McElvenny[49]	1.13 (mortality)	1.11-1.16	No control for exposure to NDEA/NDMA specifically
Straif[50]	1.4 (mortality)	1.0-1.8	Low vs. high nitrosamine exposure; not controlled for other carcinogens
Hidajat[51]	1.7-3.47 (mortality for different cancers)		No control for smoking

[49] McElvenny DM et al., *British rubber and cable industry cohort: 49-year mortality follow-up*, Occup. Environ. Med. 75(12):848-855 (2018).
[50] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).
[51] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).

None of these studies can control for all variables needed to draw any meaningful conclusion, in that cancer history, smoking, and exposure to other potential carcinogens were not accounted for, nor was the actual exposure to nitrosamines. Further, these occupational studies involved exposure through inhalation, which is not relevant to the matter at hand—i.e., oral administration of valsartan—for the reasons discussed above.

ii. *Stomach Cancer*

Plaintiffs' experts cite the following related to stomach cancer:

Study	Odds Ratio	Confidence Limits	Comments/ Criticisms
Hidajat[52]	1.72	1.41-2.10	No control for other carcinogens, such as smoking
La Vecchia[53]	1.37	1.1-1.7	Risk at daily dose of >190ng/day
Larsson[54]	1.96	1.08-3.58	Risk at doses above 194ng/day
De Stefani[55]	3.62	2.38-5.51	Risk at doses above 270ng/day
Palli[56]	1.99	1.0-3.98	Not statistically significant; NDMA exposure not clear
Loh[57]	1.13	0.81-1.57	Not significant
Jakszyn[58]	1.00	0.7-1.43	Poorly controlled

[52] *Id.*

[53] LaVecchia C et al., *Nitrosamine intake and gastric cancer risk*, Eur. J. Cancer Prev. 4(6):469-74 (1995).

[54] Larsson SC et al., *Processed meat consumption, dietary nitrosamines and stomach cancer risk in a cohort of Swedish women*, Int. J. Cancer 119(4):915-9 (2006).

[55] DeStefani E et al., *Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay*, Cancer Epidemiol. Biomarkers Prev. 5(9):679-82 (1996).

[56] Palli D et al., *Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy*, Cancer Causes Control 12(2):163-72 (2001).

[57] Loh YH et al., *N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study*, Am. J. Clin. Nutr. 93(5):1053-61 (2011).

[58] Jakszyn P, Bingham S, Pera G et al, *Endogenous versus exogenous exposure to N -nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study*, Carcinogenesis 27:1497-1501 (2006).

Keszei[59]	1.06	1.01-1.10	Poor diet questionnaire
Knekt[60]	0.75	0.37-1.51	Could not exclude a reduction of 63%
Pobel[61]	7.0	1.85-26.46	Dose above 290ng/day
Song (meta-analysis)[62]	1.34	1.02-1.76	Incorporates all the weaknesses from each study included

The meta-analysis by Song cannot exclude an only 2% increase in risk, and with reliance on questionnaires for intake (and poor control of other cancer risk factors), one cannot with confidence assign a proven cause and effect relationship with dietary NDMA and stomach cancer.

iii. *Colorectal Cancer*

Plaintiffs' experts' sources related to colorectal cancer are as follows:

Study	Odds Ratio	Confidence Limits	Comments/ Criticisms
Straif[63]	1.5 (colon) 1.6 (rectal)	0.5-4.7 0.2-3.9	No statistical difference in either
Zhu[64]	1.42 (colorectal)	1.03-1.96	Dietary study, poor control for intake
Knekt[65]	2.12 (colorectal)	1.04-4.33	NDMA amounts not specified

[59] Keszei AP et al., *Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study*, Am. J. Clin. Nutr. 97(1):135-46 (2013).
[60] Knekt P et al., *Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study*, Int. J. Cancer 80(6):852-6 (1999).
[61] Pobel D et al., *Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France*, Eur. J. Epidemiol. 11(1):67-73 (1995).
[62] Song P et al., *Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis*, Nutrients 7(12):9872-95 (2015).
[63] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).
[64] Zhu Y et al., *Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada*, Brit. J. Nutrition 111:1109-1117 (2014).
[65] Knekt P et al., *Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study*, Int. J. Cancer 80(6):852-6 (1999).

Loh[66]	0.99 (colon) 1.46 (rectal)	0.83-1.18 1.16-1.84	Poor control, no reliable intake of nitrosamines

844 iv. *Pancreatic Cancer*

845 Plaintiffs' experts cite the following in discussing pancreatic cancer:

Study	Odds Ratio	Confidence Limits	Comments/ Criticisms
Fritschi[67]	0.85	0.5-1.42	Nitrosamines not specifically evaluated
Straif[68]	No association		
Hidajat[69]	2.6 (death)	1.94-3.49	No control for smoking and other carcinogen exposure
Zheng[70]	2.28	1.71-3.04	Higher levels of estimated NDMA exposure above 240ng per day
Zheng[71]	1.03	0.78-1.37	At dietary estimated dose of 2 mcg/day

846 v. *Head and Neck Cancers*

847 With regard to head and neck cancers, Plaintiffs' experts cite:

Study	Odds Ratio	Confidence Limits	Comments/ Criticisms
Loh[72]	1.13 (esophageal)	0.77-1.68	Not significant; states an increase of 68% cannot be ruled out;

[66] Loh YH et al., *N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study*, Am. J. Clin. Nutr. 93(5):1053-61 (2011).
[67] Fritschi L et al., *Occupational exposure to N-nitrosamines and pesticides and risk of pancreatic cancer*, Occup. Environ. Med. 72(9):678-83 (2015).
[68] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).
[69] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).
[70] Zheng J et al., *Dietary N-nitroso compounds and risk of pancreatic cancer: results from a large case-control study*, Carcinogenesis 40(2):254-62 (2019).
[71] *Id.*
[72] Loh YH et al., *N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study*, Am. J. Clin. Nutr. 93(5):1053-61 (2011).

			equally so for a 23% decrease
Rogers[73]	1.82 (oral) 1.86 (esophageal)	1.1-3.0 0.87-3.95	Estimated exposure above 179ng/day
Keszei[74]	1.15 (esophageal)	1.05-1.25	15% increase per 100ng/day exposure
Straif[75]	5.1 (head/neck)	1.2-20.6	Other factors not controlled for
Hidajat[76]	3.04 (esophageal death) 1.39 (laryngeal)	2.26-4.09 0.67-2.90	No control for smoking and other carcinogen exposure
Knekt[77]	1.37 (head/neck)	0.5-3.74	Not significant

848 vi. *Liver Cancer*

849 Plaintiffs' experts' references concerning liver cancer include:

Study	Odds Ratio	Confidence Limits	Comments/ Criticisms
Straif[78]	Only 9 liver cancer deaths		Not significant
Hidajat[79]	2.86	1.78-4.59	No control for smoking and other carcinogen exposure

850 vii. *Bladder Cancer*

851 Plaintiffs' experts cite the following regarding bladder cancer:

[73] Rogers MA et al., *Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer*, Cancer Epidemiol. Biomarkers Prev. 4(1):29-36 (1995).
[74] Keszei AP et al., *Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study*, Am. J. Clin. Nutr. 97(1):135-46 (2013).
[75] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).
[76] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).
[77] Knekt P et al., *Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study*, Int. J. Cancer 80(6):852-6 (1999).
[78] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).
[79] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).

Study	Odds Ratio	Confidence Limit	Comments/ Criticisms
Jakszyn[80]	1.12	0.88-1.44	Not significant; states increase of 44% cannot be ruled out (neither can a 12% reduction)
Straif[81]	1.3	0.4-5.0	Not significant
Hidajat[82]	2.82	2.16-3.67	At higher doses

852 viii. *Prostate Cancer*

853 Plaintiffs' experts rely on the following studies with regard to prostate cancer:

Study	Odds Ratio	Confidence Limit	Comments/ Criticisms
Loh[83]	1.01	0.9-1.13	Not significant
Jakszyn[84]	1.23	0.99-1.53	Not significant
Straif[85]	2.1	0.7-1.53	Not significant
Hidajat[86]	5.36	4.27-6.73	In higher level of exposure compared to lower exposure

854 ix. *Blood Cancers*

855 Plaintiffs' experts' sources regarding blood cancers include:

[80] Jakszyn P, Gonzalez CA, Lujan-Barroso L et al., *Red meat, dietary nitrosamines, and heme iron and risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)*, Cancer Causes and Cancer Epidemiol. Biomarkers Prev. 20:555-9 (2011).

[81] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).

[82] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).

[83] Loh YH et al., *N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study*, Am. J. Clin. Nutr. 93(5):1053-61 (2011).

[84] Jakszyn PG, Allen NE, Lujan-Barroso L et al., *Nitrosamines and Heme Iron and Risk of Prostate Cancer in the European Prospective Investigation into Cancer and Nutrition*, Cancer Epidemiol. Biomarkers Prev. 21;547-51 (2012).

[85] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).

[86] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).

Study	Odds Ratio	Confidence Limit	Comments/ Criticisms
Richardson[87]	2.22	1.48-3.35	Occupational with nitrates, nitrites, nitrosamines combined
Straif[88]	Not significant		Occupational exposure estimates lacking precision
Hidajat[89]	2.25 (lymphoma) 3.47 (leukemia) 2.81 (multiple myeloma)	1.41-3.59 2.35-5.13 2.17-3.64	In higher level of exposure compared to lower exposure

856 Dr. Etminan's conclusion regarding blood cancers, in particular, appears to be simply

857 cut-and-pasted from the bladder cancer section of Dr. Etminan's report.

858 x. *Lung Cancer*

859 Plaintiffs' experts' citations regarding lung cancer include:

Study	Odds Ratio	Confidence Limit	Comments/ Criticisms
De Stefani[90]	3.14	1.86-5.29	With limitations
Goodman[91]	3.3 (men) 2.7 (women)	1.7-6.2 (men) 1.0-6.9 (women)	Dietary exposure; duration not reported
Loh[92]	1.05	0.88-1.24	Not significant
Hidajat[93]	1.7	1.54-1.87	No control for other potential carcinogenic

[87] Richardson DB et al., *Occupational risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Northern Germany*, Am. J. Ind. Med. 51(4):258-68 (2008).
[88] Straif K et al., *A review of human carcinogens– part C: metals, arsenic, dusts, and fibres*, The Lancet Oncology 10:453-54 (2009).
[89] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).
[90] DeStefani E et al., *Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay*, Cancer Epidemiol. Biomarkers Prev. 5(9):679-82 (1996).
[91] Goodman MT et al., *High-fat foods and the risk of lung cancer*, Epidemiology 3(4):288-99 (1992).
[92] Loh YH et al., *N-Nitroso compounds and cancer incidence: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study*, Am. J. Clin. Nutr. 93(5):1053-61 (2011).
[93] Hidajat M et al., *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up*, Occupational and Environmental Medicine 76:250-258 (2019).

			exposures like smoking

d. Other criticisms of and flaws in Plaintiffs' expert reports

Dr. Hecht, on page 8 of his report, lumps several studies together to opine that in several species, NDMA has demonstrated a high systemic clearance and high oral bioavailability. He cites a study by Hino et al. in his reference 21, for the proposition that NDMA was found in beagles after oral administration, suggesting to him that there is systemic bioavailability after oral NDMA exposure in larger mammals. First, the NDMA administered to the beagles in the cited study was administered intravenously and orally at a dose of 2mg/kg,[94] which would correspond to an oral dose in a typical weight (70kg) human of 140mg, or an oral dose more than 8000 times the highest NDMA amount found in any Teva valsartan product (16.55 mcg, or 0.01655 mg). Second, even smaller doses of NDMA administered to beagles would not be comparable to humans because dogs have been demonstrated to have only ¼ the CYP2E1 metabolic capacity of human 2E1, so dogs would have less capacity to clear any oral dose of NDMA than humans.[95] Thus, I disagree with Dr. Hecht's theories regarding systemic clearance and oral bioavailability of NDMA.

I also disagree with Dr. Lagana's statement on page 22 of his report that based on his review of the literature, it appears that "NDMA is absorbed into the blood." As demonstrated above, whether NDMA reaches the bloodstream is clearly dependent on the route of administration and the dose as well. Dr. Lagana's blanket statement is therefore incorrect.

[94] Hino K et al., *Salivary Excretion of N-nitrosodimethylamine in Dogs*, Eur. J. Cancer Prev. 9:271-276 (2000).
[95] Lankford SM, Bai SA, Goldstein JA, *Cloning of canine cytochrome P450 2E1 cDNA: identification and characterization of two variant alleles*, Drug Metab. Dispos. 28(8):981-6 (2000).

Notably, in Dr. Panigrahy's report on page 31, he states that "only a single dose of NDMA is required to cause and initiate cancer in multiple animal species"; however, Dr. Panigrahy does not cite to any literature in support of this assertion. Based on my experience and my review of the literature, I do not agree with Dr. Panigrahy's blanket assertion. A single dose of NDMA would be fully or almost entirely metabolized in the liver, if administered in an amount below the level that the liver is able to process, as in the case of the trace amounts of NDMA found in valsartan. NDMA would only be able to initiate cancer after a single dose if it were administered in a massive quantity, which has not been the case in any study and certainly is not the case here, where only small, trace amounts of NDMA were present in valsartan.

8. Clinical and Practical Implications of NDMA/NDEA in Valsartan

The presence of trace amounts of NDMA/NDEA in valsartan during the time period in question (i.e., 2012 to 2018) did not create any independent or increased risk of cancer in patients taking valsartan, nor did it render the medications "unreasonably dangerous." According to the FDA's NDMA guidance, the acceptable intake of NDMA is 96 nanograms (ng) a day.[96] This daily limit was estimated to be the amount that would cause a 1:100,000 cancer risk after 70 years of daily exposure. That daily amount was estimated from the dose that would induce a tumor in half of the rodents exposed in animal toxicity experiments. In most of these studies, animals received between 1-5mg of NDMA per kilogram of body weight, for both short and long-term exposure. This would be the equivalent of giving between 70 and 350mg daily to a human, which is approximately 700,000 to 3.5 million times higher than the FDA proposed

[96] *FDA Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs* at 10 (Sept. 2020).

safe upper limit of daily exposure—and still more than 4000-21,000 times higher than the highest amount of NDMA the FDA measured in any finished dose manufacturer's valsartan product(s).

Additionally, at these levels of exposure, there is no legitimate concern about whether daily ingestion could lead to some type of accumulation or saturation in the human body. That would only happen if the human body could not adequately metabolize the daily ingested amount of either NDMA or NDEA, which it is able to do at these trace amounts.

There are a few studies that have looked at the use of valsartan, at least in the short term, and the risk of cancer. In a Danish national study, during the period of 2012 (when valsartan products produced in China were first identified with NDMA) until the recall in 2018, the investigators identified 3450 patients taking valsartan that probably or possibly contained NDMA and compared the rates of cancer in these patients compared to 3625 patients taking valsartan products unlikely to contain NDMA.[97] The patients taking the probable/possible NDMA valsartan products were no more likely to develop cancer compared to the patients taking valsartan that was free of NDMA. There were two individual cancers that weakly were associated with valsartan containing NDMA (colorectal and uterine); however, the confidence limits (a measure of the uncertainty of the data) were very wide and therefore no statistical association was identified. Similarly, there were actually fewer bladder and pancreatic cancers, albeit with the same wide confidence limits, indicating no statistical likelihood of reduced cancer with valsartan NDMA exposure either. The main limitation of this Danish study was the

[97] Pottegard A et al., *Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study*, BMJ 2018;362:k3851 (2018).

relatively short period of time that patients were exposed to NDMA, approximately 4.5 years on average and ranging from 2-5 years. However, if this is the time frame of exposure to valsartan products containing NDMA/NDEA until the recall, it mimics the exposure time until these products became part of the recall. Thus, the authors conclude that any actual increased risk of cancer due to valsartan products containing NDMA/NDEA is unlikely.

Similar to the Pottegard study reviewed above, Gomm reports on a cohort study of valsartan use and cancer in the German health care system.[98] The authors suggest that exposure to valsartan products containing NDMA would have been in the time period from the change in the manufacturing process in 2012 until the recall that occurred in July of 2018. They cite a weakness in the Danish study in that only about 5000 patients were evaluated; in Gomm's analysis, a total of over 780,000 patients were evaluated, comparing cancer rates in those taking valsartan products found to have NDMA versus those taking valsartan products without NDMA. The primary study analysis was the incidence of all cancers between valsartan-with-NDMA users and valsartan-without-NDMA users. Over a mean exposure period of 3 years, the hazard ratio was 1.0, indicating that there was no difference in all cancer rates whether patients took valsartan containing NDMA or not. After adjusting for higher doses in some patients and longer durations of exposure, there was still no evidence of valsartan associated cancers. When evaluating for specific cancers, there was a statistically significant increase in liver cancers, with a hazard ratio of 1.16, and a confidence interval of 1.03-1.31. However, there was no association of liver cancer with valsartan dose, duration of exposure or variation

[98] Gomm W et al., *N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer - A Longitudinal Cohort Study Based on German Health Insurance Data*, Dtsch. Arztebl. Int. 118:357–62 (2021).

in lag time. The finding of liver cancer is in contrast with the results of the Danish study, in that the Danish study did not detect a single case of liver cancer. And, despite the study size, there was no association with NDMA-containing valsartan products and other cancers, including bladder, breast, colorectal, kidney, lung, melanoma, pancreatic, prostate and uterine.

Despite its retrospective nature, this type of trial attempts to adjust for variables they can try to control, such as matching the two groups for age and duration of exposure, among others; however the Charlson co-morbidity index was more likely in the group exposed to NDMA-containing valsartan products, making it difficult to ascribe the liver cancer risk to valsartan alone. Consistent with more NDMA-exposed patients having a higher Charlson co-morbidity index, NDMA-exposed patients had more polypharmacy, heart failure, diabetes, statin use, aspirin use and steroid use, indicating that the two groups were not equal in their background diseases or treatments. The investigators were also not able to adjust their results for differences in other cancer risk factors such as smoking status, dietary/environmental exposures and genetic predispositions. A strength of the study, compared to the Danish study, is many more patient-years of data to analyze. Despite the finding of a small increase in liver cancer, the authors conclude that this type of study only establishes a statistical association, and that causality cannot be established.

Dr. Etminan criticizes one aspect of the Gomm study that I disagree with. He contends that the Gomm study excluded cancers that occurred in the first two years, a so-called lag period, which in the three year study meant that there was, on average, only 1 year of follow-up to detect a cancer. This is a misinterpretation of the study design. Patients followed for

three years were followed for three years, not one, so the lag period did not "restart the clock" on duration of follow-up.

In July 2019, Al-Kindi published an analysis of the FDA Adverse Event Reporting System (FAERS) for spontaneous reports of neoplasms for a two year period dating from January 1, 2017 through December 31, 2018.[99] In context, the FDA recall of valsartan products containing NDMA/NDEA was in July 2018, and the FDA-announced recalls of irbesartan products and losartan products, also for the detection of NDMA/NDEA, were in October and November of 2018, respectively. The reporting from health care providers and/or consumers is completely voluntary, and these reports often fail to provide sufficient data to make any clinical judgement as to cause and effect of the reports. Al-Kindi assessed spontaneous reports of neoplasms as a percentage of all ARB adverse events reported and compared valsartan reports vs. other ARBs. Further, he evaluated whether the spontaneous reports came from health care professionals or consumers.

As would be expected, there was an abrupt increase in valsartan neoplasm reports to FAERS beginning in July 2018. Given the timing of the increased reports in relation to the date of valsartan product recalls, the authors conclude that it is biologically implausible (and I would conclude impossible) for this increase in reports to occur so quickly after the recall and is more a representation of the national media attention to the recall. They further highlight the problems with the FAERS system, which include inaccuracy of reports, delayed reports, and its passive nature, which make it an unreliable system for post-marketing surveillance of drug

[99] Al-Kindi S et al., *Abrupt increase in reporting of neoplasms associated with valsartan after medication recall*, Circ. Cadiovascular Qual. Outcomes, at 1 (2019).

safety. Al-Kindi urges for a government sponsored program of patient and provider education to avoid premature drug discontinuation, legal disputes and inaccurate drug-adverse event associations.

V. SUMMARY OF OPINIONS AND CONCLUSION

As noted above, all of the opinions that I have offered in this report are based on my education, training, knowledge, and experience in pharmacokinetics and pharmacology, as well as the materials I have reviewed in this case, and are based on grounds in scientifically valid reasoning and methodology and given to a reasonable degree of scientific certainty. As reflected above and summarized below, these are my opinions concerning this case, and I have a sufficient factual basis and good grounds for my conclusions:

i. I have analyzed the pharmacokinetic characteristics and pharmacology of valsartan.

ii. I have also analyzed the pharmacokinetic characteristics and pharmacology of NDMA and NDEA, including a comprehensive review of the published potency data.

iii. I have read and reviewed the reports, opinions, and references cited by Drs. Mahyar Etminan, Stephen Hecht, Stephen Lagana, and Dipak Panigrahy in this litigation, and I disagree with their conclusions and opinions concerning the pharmacology and pharmacokinetics of NDMA and NDEA. I have outlined many of my criticisms of those conclusions and opinions above, but this report is not intended to be an exhaustive recitation of all of my criticisms of the reports and opinions of Drs. Etminan, Hecht, Lagana, and Panigrahy.

iv. The ANDA for valsartan is valid, and there has been no requirement for a new ANDA. The efficacy and bioequivalence of valsartan are not altered by the presence of NDMA or NDEA.

v. Based on my analysis of their pharmacokinetic properties, my extensive review of the scientific literature, and my own research and the research of others on this very issue, it is my opinion to a reasonable degree of scientific certainty that the level of NDMA and/or NDEA found in the valsartan drugs at issue would not be circulated beyond the liver and would not reach organs that are not part of the digestion / metabolism process.

vi. It is my opinion to a reasonable degree of scientific certainty that the scientific evidence does not support a causal association between exposure to the very low levels of NDMA and/or NDEA impurities detected in valsartan and any of the cancer types alleged by Plaintiffs.

vii.. The scientific literature and evidence, which I have reviewed extensively, do not support that the valsartan products, during the time period at issue, carried an independent risk of cancer, nor that there is any increased risk of cancer associated with the valsartan containing the NDMA/NDEA impurity as compared to valsartan with a zero level of NDMA/NDEA.

viii. It is my opinion that no scientific professional could credibly claim to a reasonable degree of scientific certainty that Plaintiffs' cancer was caused by their treatment with any valsartan product containing trace levels of NDMA/NDEA impurities during the time period in question.

I may use at trial any exhibits as a summary or in support of all of my opinions, including but not limited to: (1) any of the materials, or excerpts therefrom, identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; and (5) any exhibit used in or identified at any deposition taken in this litigation. If further data becomes available, I reserve the right to review it and consider whether to modify any portion of these opinions.

Dated: August 2, 2021

Michael Bottorff, Pharm.D., FCCP, FNLA, CLS